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VASCULAR ALLERGY. III

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THE present report deals with a continuation of the investigations of a special group of sixteen cases of bronchial asthma observed since 1936, eight of which have been previously recorded.[1] Four of these patients died, and their necropsy findings form an essential feature of this communication. The clinical course of the sixteen patients was closely similar in most respects except for the degree and number of shock tissues involved. Each one gave a history of repeated winter colds. A family history of allergy was present in five patients, and in seven, two of whom came to autopsy, there was a personal history of allergy. Chronic infection of the sinuses was present in each instance. The latter was regarded as the possible source of bacterial sensitization which could have played a role in the precipitation of the asthmatic attacks. In six cases where an attempt was made to identify the bacteria involved, the observed cutaneous and systemic reactions to pneumococcus polysaccharides and autogenous vaccines prepared from the flora of sinus washings seemed to suggest some relationship to the presenting symptoms.

Patient 5 (Table I), whose sputum contained pneumococcus Type VI, was tested with ten different pneumococcus polysaccharide fractions according to the standard technique, and showed immediate positive reactions to the polysaccharides of pneumococci Types V and XIV, but none to Type VI. Nevertheless, precipitins* for pneumococcus Type VI and agglutinins for pneumococcus Type XIV were demonstrable in the blood serum. Eight hours later, reddish nodules similar to tuberculin reactions appeared in the areas injected with the polysaccharide substance of pneumococci Types V and XIV, and the patient developed a severe generalized urticaria which lasted for three days.

Patients 7 and 9, whose bronchial secretions contained pneumococci Types V and III respectively, and Patient 15, from whose sputum pneu-

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*The serological reactions were made at the Harlem Hospital through the courtesy of Dr. Jesse M. Bullowa.

TABLE I

CASE	AGE (YEARS)	FAMILY HISTORY OF ALLERGY	PERSONAL HISTORY OF ALLERGY	SINUS DISEASE	ASTHMA	LONG INFILTRATION	SPUTUM EOSIN	SINUS AND SPUTUM BACTERIA	*HB*	*R.B.C.*	*W.B.C.* (MAXIM.)	BLOOD EOSIN (MAXIM.)	SKIN TESTS
1, F. B.	21	Present	Present	Present	Occasional: cough mostly	Recurrent from 1932 to 1939, upper and lower lobes	Present	*Staph. aureus*	66%		32,000	54%	Positive to foods and pollen
2, S. G.	42	Negative	Repeated colds	Present	3 years	Upper and lower lobes	Present	Pneumococci, streptococci, Vincent's spirilla	90%		16,500	63%	Positive to foods and pollen
3, L. G.	48	Present	Repeated colds	Present	2 years	Both lower lobes	Present	*Strep. hemolyticus* *Strep. viridans*	63%		24,300	47%	Positive to foods, dust and tobacco
4, D. Z.	26	Negative	Negative	Present	None except cough and bloody expectoration	Upper lobes	Present	*Staph. aureus* *Strep. viridans*	73%	4.6 mil.	21,800	65%	Positive to foods and pollen
5, M. M.	22	Present	Present	Present	2 years	Both upper lobes	Present	Pneumococcus Type VI	66%		14,900	49%	Positive to pneumo. polysacch. Type V, XIV. Negative for Type VI
6, J. S.	26	Negative	Negative	Present	2 years	Both upper lobes	Present	— —	87%	4.5 mil.	21,000	46%	Pollens and foods
7, E. E.	26	Present	Present	Present	10 years	Right upper and lower lobes	Present	Pneumococcus Type V, *Strep. viridans*	85%		17,000	85%	Pollens and foods. Positive to pneumo. Type V, polysacch.
8, G. R.	39	Present	Repeated colds	Present	4 years	Negative	Present	— —	80%		8,600	16%	Pollens and foods.
9, L. C.	26	Negative	Repeated colds	Present	4 years	Right upper lobe scattered throughout rest of lung	Present	Pneumococcus Type III, *Strep. hem. B.*	54%	3.1 mil.	36,000	68%	Positive to pneumo. Type III, polysacch.

10. P. D.	41	Negative	Present	Present	3 years	Left and right lung	Present	*Staph. aureus, M. catarrhalis, Strep. nonhemolyticus*	60%		40,000	50%; bone marrow eosin*	Positive to foods, pollen and dust
11. B. S.	32	Negative	Repeated colds	Present	4 years	Fibrosis throughout	— —	— —	70%		18,000	40%	Negative
12. E. G.	19	Negative	Present	Present	3 years	Right upper and lower lobes	Present	*Strep. viridans, M. catarrhalis*	75%		20,000	39%	Positive to dust and pollen
13. M. B.	38	Negative	Negative	Present	4 years	Infiltration in both central fields	Present	Pneumococci, Strep. hemolyticus, *Staph. aureus and albus*	72%	5.3 mil.	19,000	39%	Negative
14. S. S.	18	Negative	Present	Present	4 years	Right and left lower lungs	Present	*Staph. aureus*	60%		25,000	44%; bone marrow eosin*	Positive to foods and pollen
15. F. H.	21	Negative	Present Eczema in infancy	Present	5 years	Left lung lower and upper	Present	Pneumococcus Type III, *Staph. aureus, Strep. viridans*	85%		40,000	50%; bone marrow eosin*	Positive to pneumo. Type III, polysacch.
16. K. W.	35	Negative	Negative	Present	6 years	Infiltration both lower lobes	Present	— —	80%	4.02 mil.	70,000 in 1938; 16,500 in 1942	82% None	Not tested

*Increased eosinophilia in the bone marrow.

(See continuation of Table)

TABLE I—CONT'D

CASE	HEART	ELECTROCARDIOGRAM	PLEURAL EFFUSION	PERI-CARDITIS	PERI-TONEAL EFFUSION	SKIN LESIONS	SKIN BIOPSY	POLY-ARTHRITIS	COMPLI-CATIONS	RESULTS
1	Negative	Not studied	Present	--	--	--	--	--	--	Well
2	Negative	Not studied	Bilateral eosinophilic	--	--	--	--	--	--	Well
3	Negative	T semi-inverted in Lead I; T_2 and T_3 inverted	--	--	--	--	--	--	--	Well
4	Negative	L.V.P. Q wave present in Lead I; T_3 inverted, T_1 isoelectric	Bilateral eosinophilic	--	--	Necrosis of skin in Scarpa's triangle in right thigh	Acute diffuse inflammation with eosinophilia	--	--	Well
5	Negative	T_1, T_2 low, T_3 and T_1 isoelectric	Bilateral eosinophilic	--	--	Urticaria	--	--	--	Well
6	Negative	Not done	Present	--	--	--	--	--	--	Well
7	Negative	QRS low in Lead I, high in Leads II and III	--	--	--	--	--	--	--	Well
8	Transverse enlargement	P-wave enlargement; T_2 and T_3 inverted	--	--	--	Nodules on upper and lower conjunctivae	Biopsy of nodule from conjunctiva shows collagen necrosis with giant cell reaction and eosinophilic infiltration	--	--	Early cardiac decompensation
9	Tachycardia	QRS low; T waves diphasic	--	--	--	Subcutaneous nodules	Necrotizing arteritis	Present	--	Still sick

10	Tachycardia	QRS notched in Lead II; Q wave present in Lead III; T waves isoelectric in all leads	Present eosinophilic	--	Eosinophilic ascites	--	--	Present	--	No follow up
11	Right heart enlarged	QRS complexes slurred, of low voltage; T waves in Lead I, II and IV inverted	Present	Adhesive	Eosinophilic ascites	Urticaria, purpura and angioneurotic edema	Diffuse perivascular and perineural infiltration with eosinophilic infiltration of purpuric lesion	Present	Enlarged liver with distension of abdominal veins; icterus	Exitus, cardiac failure
12	Transverse enlargement	QRS low in Lead I; trigeminal rhythm	Present eosinophilic	Adhesive	Present	Purpura. Papular necrotic tuberculid showed collagen necrosis with giant cell reaction and fibroblastic proliferation	Purpuric spot showed severe inflammation with infiltration of blood vessels and nerves with eosinophiles	Present	Ulcerative colitis	Exitus cardiac failure
13	Transverse enlargement	Low voltage of T waves throughout A.V. block	Present eosinophilic	Adhesive	Present	Urticaria, angioneurotic edema, subcutaneous nodules	Nodules showed arteritis and periarteritis nodosa	Present	Amyloidosis of liver, albuminurea	Exitus, acute pneumonia and cardiac failure
14	Transverse enlargement	QRS slurred, low voltage; RST depressed Lead I; T_1 and T_2 flat, T_3 inverted	Present eosinophilic	Adhesive	--	Purpura, subcutaneous nodules	Nodule showed collagen necrosis and giant cells of foreign body type, necrotic foci with eosinophilic infiltration	--	Hypertension and renal involvement	Exitus, cardiac failure, uremia
15	Negative except during acute pericarditis	QRS low; T wave low in Lead I, II and III; T_1 inverted	Present	Adhesive	--	Purpura, papular erythema	Perivascular infiltrations with eosinophiles	Present	Ulcerative colitis	Exitus, cardiac failure
16	Negative	QRS slurred, low voltage; T_1 isoelectric, T_2, T_3 low, T_4 inverted. RT_4 depressed, intraventricular block	Present	Adhesive	Present	Purpura	--	--	Anasarca	Exitus, cardiac failure

mococcus Type III was cultured, were tested with the same number of polysaccharide fractions and gave immediate positive reactions to the corresponding polysaccharide fractions of these organisms. Both precipitins and agglutinins for pneumococci Types V and III were present in the sera of Patients 7 and 9. Twenty-four hours later, delayed inflammatory nodules also occurred in these two patients at the sites of the previous immediate positive reactions. They were accompanied by exacerbation in the asthmatic attacks. Patient 15, examined in the midst of an asthmatic paroxysm, was not studied serologically.

Inasmuch as 40 per cent of normal individuals show an incidence of positive skin reactions to various polysaccharides of the pneumococci, indicative of some previous infection with these organisms, the thought suggests itself that in these cases, also, some infection with these or related organisms may have played a role in the presenting symptoms.

In Patient 10, the intracutaneous injection of an autogenous vaccine derived from the sinus washings, consisting of *Staphylococcus aureus A.*, *M. catarrhalis*, and *Streptococcus nonhemolyticus*, and, in Patient 14, one containing *Staphylococcus aureus A.* only, were also followed by systemic reactions. The former developed a severe asthmatic seizure and shock, and the latter, pulmonary infiltration accompanied by fever, cough, generalized petechiae, and ecchymoses in the left calf. These, as well as the urticaria in Case 5, were the external manifestations of a vascular response dependent upon hypersensitiveness to the injected bacterial products.

Positive reactions to foods, pollens, and inhalants were also present in eleven of the sixteen patients. Only in seven were they found to be of clinical significance in conjunction with the bacterial hypersensitiveness (Table I).

CLINICAL MANIFESTATIONS

Bronchial asthma was the cardinal presenting symptom in fifteen of the sixteen cases. Patient 4 in this group was admitted to the surgical service because of a brawny infiltration in the thigh which proved on biopsy to be an eosinophilic inflammation. Coincidentally, this patient developed interstitial pulmonary infiltrations similar in every respect to the fugitive and migratory lesions resembling tuberculosis which were observed in the asthmatic patients. The pulmonary infiltrations fluctuated with the asthmatic attacks. In most instances, the pathologic changes in the lungs were not detectable by physical signs but were revealed by x-ray examination exclusively. This was probably due to the interstitial nature of the infiltrations.

In eight of the sixteen cases, in conjunction with the pulmonary lesions there developed sterile pleural effusions in which marked eosinophilia was demonstrable. Concurrently, there also appeared electrocardiographic abnormalities involving the auricular and ventricular complexes. These were, in the main, not associated with any auscultа-

tory or other clinical evidence of cardiac involvement, with the exception of those cases who developed either pericarditis or signs of cardiac decompensation. In the patients who recovered, both the pleural effusions and the electrocardiographic changes were reversible, only to recur with the reappearance of asthmatic attacks. Consequent upon the development of an acute pericarditis in Case 15, the asthma temporarily disappeared and, instead, there developed urticaria and polyarthritis. The latter was suggestive of rheumatic fever except that in this instance there was persistence of high blood eosinophilia. With the subsidence of the acute pericarditis, the asthma returned. In the cases which came to a fatal termination, the inflammation in the pericardium became chronic, and, together with the progressive lesions in the myocardium, gave rise to enlargement of the cardiac outlines and various murmurs, as well as irreversible electrocardiographic changes (Cases 11 to 16). Three of these patients, Cases 11, 12, and 13, developed signs and symptoms of constrictive pericarditis and, with the appearance of eosinophilic exudates in the pleura and peritoneum, the syndrome of polyserositis. A fourth patient, Case 16, also developed the syndrome of polyserositis, and eosinophiles were demonstrable in the pleural fluid on one occasion, whereas there were none in the ascitic fluid.

Other salient features were polyneuritis in four patients, and various skin lesions in the nature of urticaria, purpura, papular erythema, and angioneurotic edema, (Table I).

LABORATORY DATA

Bronchoscopy in Cases 5, 7, and 9 disclosed pale swollen mucous membranes with mucoid secretions in which eosinophilia predominated. On culture, the bronchoscopic aspirations yielded pure strains of pneumococci VI, V, and III, respectively. The sputum examinations of the other cases disclosed a variable flora consisting of pneumococci, *Streptococcus hemolyticus, Streptococcus viridans, Staphylococcus albus, Micrococcus catarrhalis,* Vincent's spirilla, etc. Washings from the sinuses yielded on culture, in some cases, pneumococci, and, in others, *Staphylococcus aureus hemolyticus, Staphylococcus albus, Streptococcus viridans, Staphylococcus aureus,* and *Staphylococcus citreus* (Table I). The blood counts were characterized by the number of leucocytes ranging from a minimum of 7,000 to a maximum of 40,000 and by the percentage of eosinophiles ranging from 7 to 84 per cent. Bone marrow obtained by sternal puncture in three cases showed a marked increase of eosinophiles. Blood cultures taken in five cases were reported as sterile. The pleural and peritoneal fluids were also sterile on culture, the specific gravity was about 1015, and the eosinophile count varied from 85 to 100 per cent in the majority of cases.

The four patients of this group who came to autopsy were Cases 13, 14, 15, and 16.

CASE HISTORIES

CASE 13.—M. B., aged 38 years, was admitted to Montefiore Hospital, May 9, 1935. His family and past history was negative for allergic diseases.

The present illness began in August, 1931, after exposure in an ice-box for twenty minutes. During the night he developed a severe chill, pain in the right side, shortness of breath, cough, and expectoration. This persisted for three weeks and was followed by asthma which continued intermittently through 1932. In the summer of 1933 there was a recurrence of pain in the back, loss of weight, night sweats, and bloody expectoration together with severe asthma. In July, 1934, a sudden onset of pulmonary edema, orthopena, and cyanosis necessitated his admission to the New York Post Graduate Hospital, where it was discovered that he had a bilateral hydrothorax, which required repeated tapping. Examination of the chest fluid showed it to be sterile both on culture and following guinea pig inoculations. X-ray examination of the chest and sinuses disclosed the following: the lung-fields contained scattered infiltrations, marked root branch fibrosis, bronchial thickening, and bilateral hydrothorax. All the sinuses were found to be involved.

The condition of the patient improved slowly, the hydrothorax, subsided, but the asthma continued. Repeated blood examinations were marked by constant eosinophilia. Biopsy of a lymph node because of a generalized lymphadenopathy showed chronic lymphadenitis with a high degree of eosinophilia. The electrocardiogram disclosed low voltage and T-wave changes indicative of myocardial damage.

Skin tests for sensitivity to foods and inhalants were essentially negative. The patient was discharged in December, 1934, improved.

After an interval of several weeks, he returned to the New York Post Graduate Hospital with a recurrence of all the previously noted symptoms. X-ray films of the chest in March, 1935, were interpreted as showing extensive "fibrobronchiectatic infiltrations in the lower lobe and right central lung field, pleural thickening and exudate at both bases, and general organized central bronchopneumonic infiltrations." The electrocardiogram showed a rapid heart rate, right axis deviation, low voltage, and first stage auriculoventricular block.

He remained at the Post Graduate Hospital until March 9, 1935, improving steadily, and was discharged with the diagnosis of "bronchial asthma, chronic pansinusitis, myocardial disease secondary to emphysema, and chronic generalized lymphadenitis."

The remission in his symptoms was short-lived. He was admitted to Montefiore Hospital on May 5, 1935, emaciated, coughing, and orthopneic. Physical examination revealed bilateral hydrothorax. There was generalized wheezing throughout both lungs. The heart was somewhat enlarged both to the right and left, and occasional premature beats were heard. The liver was enlarged, the spleen was palpable, and there was clubbing of the fingers and toes, as well as acrocyanosis.

X-ray examination confirmed the presence of fluid at both bases and a considerable amount of pulmonary fibrosis, more at the right than at the left base. The heart showed definite enlargement of the pulmonary conus.

The fluid was removed and found to contain large numbers of eosinophile cells, but it was bacteriologically sterile.

During a continued stay at the hospital, in addition to his asthma and hydrothorax he developed fugitive joint pains in the upper and lower extremities together with a temperature of about 100° F. X-ray examination of the joints was negative. During the period of arthritic manifestations, the asthmatic seizures diminished, averaging about two a night. In view of the blood eosinophilia, which varied between 18 and 28 per cent, a biopsy of a piece of muscle was made to rule out trichinosis. On section the muscle bundles appeared to be densely infiltrated with lymphocytes and eosinophilic leucocytes with no signs of trichinae.

In December, 1935, the patient began to show evidence of a peripheral neuritis. Skin manifestations characterized by erythema, multiforme-like lesions, angioneurotic edema, urticaria, and small subcutaneous nodules, supervened. A diagnosis of periarteritis nodosa was made. Biopsy studies of one of the nodules confirmed this opinion.

The subsequent course was as follows: In February, 1935, he developed a purpuric eruption over his feet and ankles.

On May 23, 1936, there was a remission of the skin lesions and a disappearance of the subcutaneous nodules. The asthma, however, together with cough and blood-streaked sputum increased in severity until about Sept. 15, 1936, when it gradually subsided. In October there was an acute exacerbation of his sinusitis associated with an acute otitis media. Following this, he developed precordial distress and anginal pains.

In February, 1937, the patient suddenly acquired severe pain in the right upper quadrant of the abdomen. The liver was found to be markedly enlarged and tender. A diagnosis of periarteritis nodosa of the vessels of the liver was made, associated with passive congestion secondary to cardiac decompensation. Early in March of the same year the angioneurotic edema previously noted recurred, and asthma and pain in the left chest returned. X-ray films, on March 17, 1937, disclosed massive infiltration in the lungs, especially in the left upper lobes, not present in January, 1937. On April 20, 1937, there was a regression of the pulmonary lesions and the pleural effusions at both bases. The heart shadow appeared to have become enlarged to the right. This was interpreted as probably due to a pericardial effusion (Figs. 1 and 2). The enlarged liver, which now reached the umbilicus, together with the presence of peripheral edema, attested to the increasing congestive failure.

In June, 1937, the patient's condition became worse. Marked albuminuria supervened, with occasional casts. The urine showed a specific gravity of 1007. Blood examination disclosed hypoproteinemia and

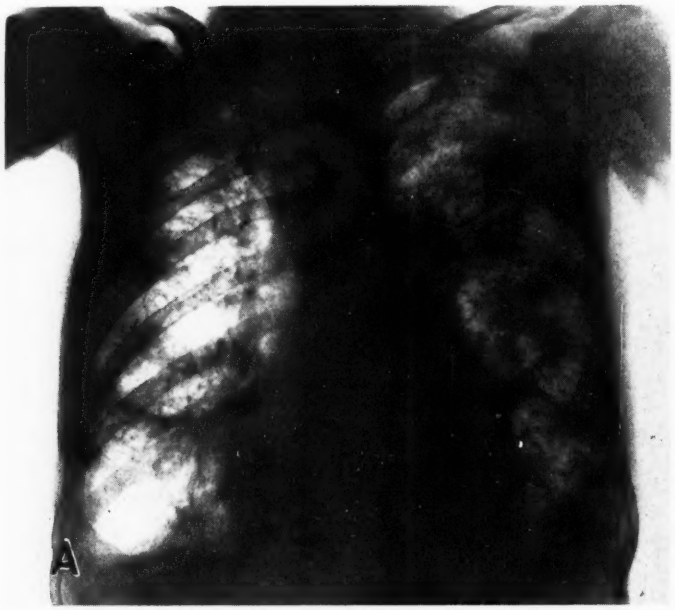

Fig. 1.—Case 13. March 17, 1937. Diffuse interstitial infiltration, with an area of consolidation in the upper lobe of the left lung and a small pleural effusion. The heart is enlarged to the right.

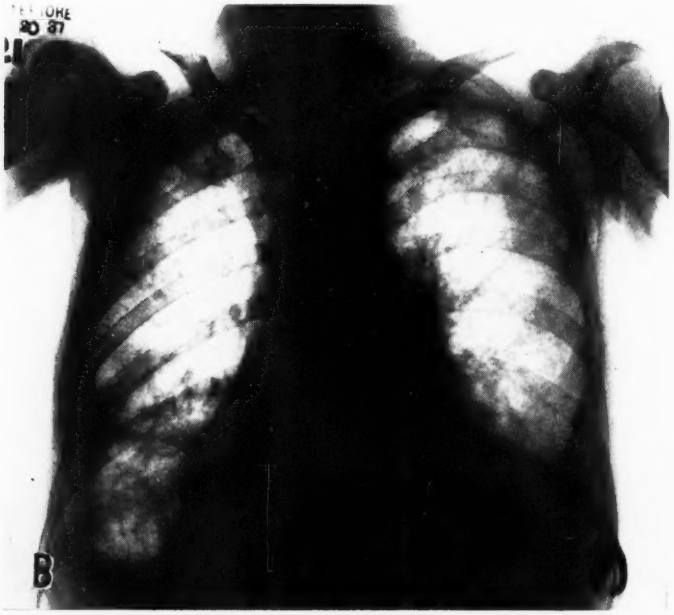

Fig. 2.—Case 13. April 20, 1937. Almost complete absorption of pulmonary infiltrations and the bilateral effusion. The cardiac shadow is enlarged.

alteration in the serum-globulin ratio. The total protein was 5.1 Gm., albumin 2.0 Gm., globulin 3.1 Gm., cholesterol 223 mg., and the urea nitrogen 10.9 mg. per cent. The hemoglobin was 72 per cent, Red Blood Cells 4,300,000. The white blood count was 14,000 and 21 per cent eosinophilia. This nephrotic picture together with the enlarged liver was interpreted as probably due to amyloidosis. A congo red test, disclosing 100 per cent retention in five minutes, confirmed the diagnosis.

On Dec. 14, 1937, the patient experienced a sudden sharp pain in the right upper chest, together with bronchial breathing in the right upper lobe of the lungs, suggestive of an acute pneumonic process. The next day the pain shifted to the upper lobe. Examination of sputum yielded pneumococcus Type XIX. Petechiae appeared over both hands and feet. The heart sounds became progressively inaudible. The patient grew steadily worse and lapsed into coma. The blood count on this occasion rose to 18,350 white cells with 92 per cent polymorphonuclears. The eosinophiles had completely disappeared. Death came Dec. 22, 1937, two years and five months after admission.

Necropsy: Macroscopic Examination.—Chronic bronchitis with emphysema; interlobar empyema on the left side, adhesive pleuritis; bronchopneumonia; obliterative pericarditis; abscesses of the pericardium; hypertrophy and dilatation of the right auricle and ventricle; chronic mediastinitis; gross amyloid disease of the liver and kidneys; fatty degeneration and cloudy swelling of the kidneys; acute splenic tumor.

Microscopic Examination: Lung: Left upper lobe and right lower lobe disclosed an acute purulent pleuritis, as well as pleural thickening by edematous fibrillar connective tissue, showing some fibrinoid necrosis, congestion, and infiltration with neutrophiles, eosinophiles, lymphocytes and plasma cells, large mononuclears and fibrocytes. The lung tissue was atelectatic and congested. Selerosis of small vessels was present. The right upper lobe showed some areas of pneumonia, edema, and thrombi in small vessels. There was marked edema of the bronchial walls, infiltration with polymorphonuclear leucocytes, lymphocytes, plasma, and eosinophilic cells, together with thickening of hyaline basement membrane characteristic of bronchial asthma.

Pericardium and heart: The pericardium was thickened by hyaline fibrous tissue, and the outer layer was infiltrated with lymphocytes, plasma cells, mononuclear cells, and delicate fibrillar connective tissue strands. Many congested new capillaries, occasional eosinophilic leucocytes, as well as sclerosis of small vessels were present. There was seen, also, slight myocardial perivascular fibrosis and interstitial edema.

Sections through the right ventricle including the pericardium disclosed moderate-sized pericardial abscesses rich in polymorphonuclear leucocytes and fibrin, surrounded by organized chronic inflammatory tissue. There was diffuse acute inflammation superimposed on chronic granulation tissue. The exudate showed many eosinophiles. There

was slight myocardial hypertrophy, interstitial fibrosis and edema, and occasional lymphocytes and polymorphonuclear leucocytes in the trabeculae and endocardium. Marked thickening of several small arteries with evidence of arteritis, perivascular fibrosis, and lymphocytic infiltration was seen.

Liver: There were extensive amyloid deposits in the central portions of the lobules. The hepatic artery showed a marked narrowed lumen due to fibrous thickening. The arterial walls were also infiltrated with occasional polymorphonuclear leucocytes, lymphocytes, and old blood pigment. There was perivascular fibrosis which extended to the biliary ducts, and many new capillaries as well as islands of polymorphonuclear leucocytes and lymphocytes were present. This lesion was consistent with healed periarteritis nodosa.

The spleen and pancreas did not disclose any important findings. The adrenals showed some areas containing amyloid deposits.

The kidneys showed extensive amyloidosis with replacement of the largest portion of every glomerulus. There were few hyalinized glomeruli with corresponding small scars. Amyloid was present in the walls of the small vessels and between the tubules of the medulla. Conspicuous cloudy swelling of the epithelium of the convoluted tubules, and deposits of fat were also evident.

Diagnosis, by Dr. David Perla, was "periarteritis nodosa."

Case 14.—S. S., female patient, aged 8 years, was admitted to Dr. Schick's service, Mount Sinai Hospital, Aug. 8, 1938, with the history of attacks of bronchitis beginning at the age of 3 years. On one occasion she was given an inoculation of "cold serum" which was followed by a severe asthmatic attack. A diagnosis of bronchial asthma associated with chronic sinusitis was made. Following the first injection of a vaccine made from sinus washings, a severe bronchitis with asthmatic attacks supervened, accompanied by recurrent nose bleeds. This continued for two weeks, associated with temperature ranging to 103° F. Skin tests showed her to be sensitive to cat and dog hair as well as to ragweed pollen. On admission to the hospital, she appeared to be chronically ill and orthopneic. She had a barrel chest with numerous sonorous and sibilant râles. The heart sounds were weak. Blood pressure was 110/84 mm. Hg. The electrocardiogram showed sinus tachycardia with a rate of 140, QRS slurred of low voltage, RST transition depressed in Lead I, T_1 and T_2 flat, T_3 inverted. The hemoglobin was 92 per cent, red blood cells 4,100,000, white blood cells 17,200, with 49 per cent eosinophiles, 1.5 per cent basophiles, 4.5 per cent monocytes, and 16.5 per cent lymphocytes. The blood culture was normal. The bone marrow puncture yielded numerous eosinophiles. Urine showed faint trace of albumin and occasional white blood cells. The concentration power of the kidneys was normal. The blood chemistry was normal. X-ray of the chest showed irregular infiltrations at

the root of the right lung extending at the right base. All the sinuses were cloudy. The nasal smear showed numerous eosinophiles. The sinuses were irrigated, and an autogenous vaccine of *Staphylococcus aureus A.* was made. Two days after the first injection of 0.01 c.c. of the vaccine intradermally, she developed numerous petechiae over the body as well as in both conjunctivae. The left calf of the leg showed a large area of ecchymosis. The tourniquet test at this time was positive. Examination of the lungs disclosed diminished breath sounds and numerous fine râles over the right base. The temperature rose to 102° F. The heart showed tachycardia, and the blood pressure was 116/90. The petechiae continued to recur. The child was doing poorly. The hemoglobin fell to 60 per cent. The urine began to show casts.

Because of the continuous asthma and general condition, a right nasal antrotomy was performed. The patient bled considerably and developed a follicular tonsillitis following the operation. The blood pressure continued to be elevated to 142/110. Fundus examination disclosed a large exudate in the right retina. On September 15, the thirty-ninth day of hospitalization, she complained of headache in the right parietal region, epigastrium, and right loin. This was followed by twitching of the left cheek, and a jacksonian convulsion of the left upper extremity which spread to the entire left side of the body. The blood pressure during this seizure ranged from 200 to 290 systolic, and 120 to 130 diastolic. A lumbar puncture showed an initial pressure of 180 mm. which rose to 260 upon pressure of both jugulars. Injection of 60 c.c. of 2 per cent magnesium sulfate intravenously caused the blood pressure to fall to 155/100. The pulse dropped from 200 to 140, and the patient was somewhat improved. The convulsion was explained on the ground of the hypertension, similar to that observed in hypertensive encephalopathy. The eye grounds showed moderately severe hypertensive retinitis. The following day, she was still sick and developed pulmonary edema. This was relieved by phlebotomy and aminophylline.

Throughout this period, the asthmatic attacks varied in intensity and were somewhat controlled by aminophylline. It was noted that chocolate, egg, fish, wheat, and milk were frequently the cause of asthmatic attacks.

Injection of a mixture of autogenous and stock vaccine was again tried. Two to three days after the first injection, she developed a temperature of 102° F. which persisted off and on for two weeks, together with asthmatic seizures. After a time she began to improve and was discharged on Dec. 20, 1938, four months after admission. She went to Tuscon. While there, for three months, she continued to have daily attacks of asthma with little relief. Thence, she went to Los Angeles for two months, with no change in symptoms.

She returned to the hospital in July, 1939. Examination of the lungs showed the presence of asthma. X-ray examination disclosed dense

pneumonic infiltration in the right upper lobe and the left base. The remaining lung fields showed marked accentuation of the hilar and bronchovascular shadows with mottled infiltration throughout. The blood pressure was 130/100. The albuminuria persisted. She continued to develop petechiae and small hard subcutaneous nodules. The cervical, axillary, and inguinal nodes were shotty. Biopsy of one of the subcutaneous nodules showed scattered collagen necrosis and a few giant cells of the foreign body type, secondary calcification of necrotic foci, and eosinophilic infiltration. She remained in the hospital for four and a half weeks and was discharged Aug. 18, 1939.

She was readmitted Nov. 7, 1939, for the third time. Since her last discharge she had continued to do badly. Asthmatic seizures persisted. The subcutaneous nodules previously noted recurred and regressed in various parts of her body including the scalp. The blood pressure was still high. Hemoglobin was 6.7 mg., red blood cells 3,000,000, white blood cells 25,000, with eosinophiles 20 to 44 per cent. Skin biopsy from the anterior abdominal wall showed connective tissue undergoing collagen necrosis with epithelioid cell and foreign body giant cell reaction accompanied by a conspicuous eosinophilic infiltration.

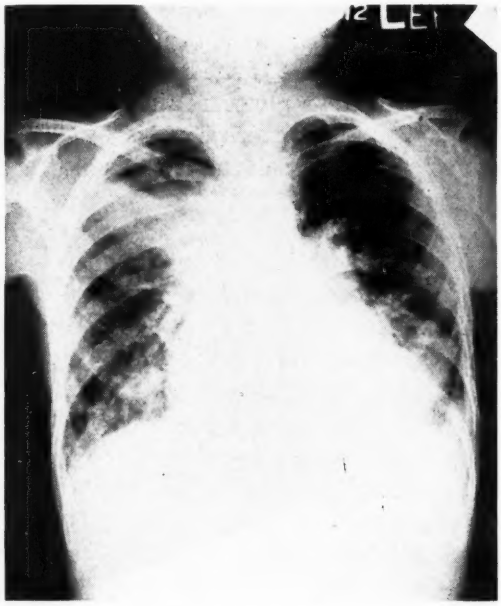

Fig. 3.—Case 14. Infiltrations throughout both lungs, confluent in right upper and left lower bases. Heart enlarged.

A diagnosis of periarteritis nodosa was made. She left the hospital Dec. 23, 1939, only to return on Jan. 9, 1940. At this admission, the most striking clinical symptom was marked heart failure. This was evidenced by pulsating dilated veins, enlarged liver, edema of the face and ankles, and râles in the chest. The peripheral vessels were sclerotic. Digitalization was started. On the third day she developed a convulsion

involving the right side of her body, which spread to the left. Magnesium sulfate was injected without any effect on the blood pressure. She died without regaining consciousness.

This patient presented a variety of symptoms referable to (1) the lungs expressed as asthma, (2) the heart terminating in and manifested by hypertension, gallop rhythm, tachycardia, and electrocardiographic changes, (3) the kidneys demonstrated by albuminuria, casts, and hypertension, (4) the skin characterized by petechiae, ecchymoses, positive fragility test, and (5) the brain evidenced by epileptiform seizures.

Necropsy: Macroscopic Examination.—Chronic passive congestion of lungs; left hydrothorax, bilateral pleural adhesions; myofibrosis cordis; fibrinous and fibrous pericarditis; congenital hypoplasia of the right ventricle of the heart; small infarction in the liver; vascular atrophy of the kidney; and skin nodules which microscopically showed collagen necrosis.

Microscopic Examination.—Lung: Pulmonary edema, areas of thickened septa, and atelectasis were present. Bronchi showed hyalinized basement membrane. Vessel walls had thickened intima and infiltrations. Arterioles were surrounded and infiltrated by cuff of round cells and occasional polymorphonuclear cells. Arteries were present which showed infiltration and degenerated areas surrounded by granulation tissue with many eosinophiles (Fig. 4).

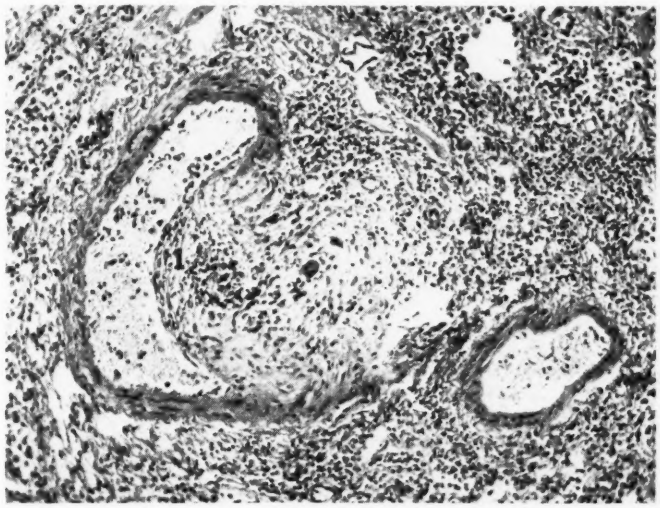

Fig. 4.—Case 14. Necrotizing arteritis of a pulmonary artery surrounded by eosinophile cells.

Heart: Microscopic areas of myofibrosis were present. There were atrophy and degeneration of muscle fibers. An area between auricle and ventricle shows mild cellular infiltrations consisting of polymorphonuclear leucocytes, plasma cells, and lymphocytes. In the left auricle were areas of necrosis and giant cell reaction. Epicardial fibrosis with

granulation tissue was present, as well as marked endocardial thickening. In the right ventricle a vessel wall with complete obliteration, infiltration of all layers, surrounded by eosinophiles, was seen. The aorta showed areas of adventitial collagen necrosis with granuloma formation and giant cells. Thickened intima showed fat.

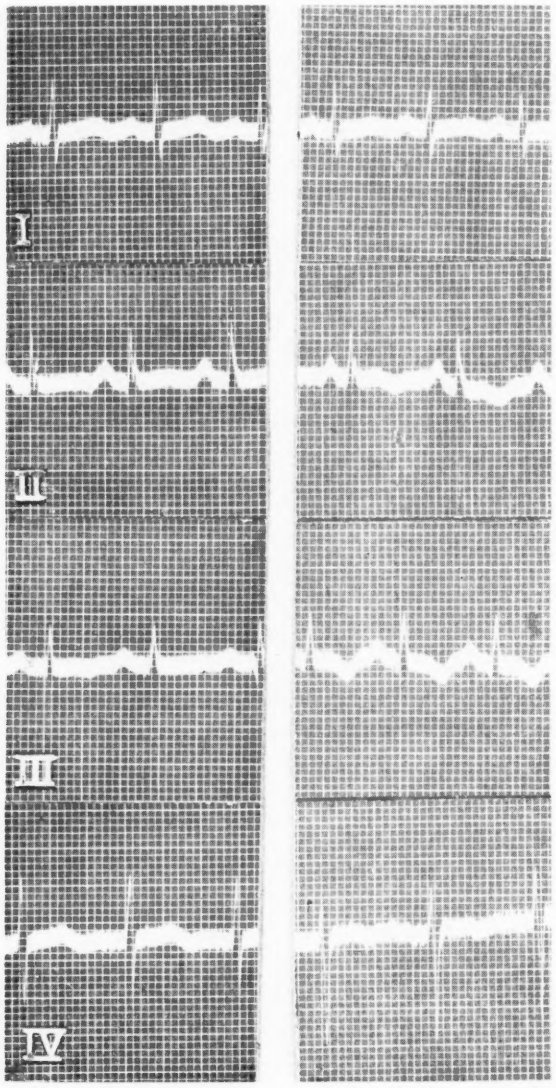

Fig. 5.—Case 15. *A*, Electrocardiogram made July 1, 1937, during an attack of asthma. The T waves are isoelectric in Leads II and III, and the QRS complex is notched in Lead II. *B*, Electrocardiogram made Nov. 14, 1938, at the termination of an episode of acute pericarditis with asthma. The T waves are inverted in Leads I, II, and III, and the voltage of the QRS complex is lowered.

Diagnosis.—Periarteritis nodosa involving heart, liver, gall bladder, kidneys, intestine, bladder (microscopic), and periaortic tissue (microscopic).

Comment (by Dr. Paul Klemperer).—"This was a very typical case of periarteritis nodosa. There was, in addition, a very unusual picture to which attention was directed during life, i.e., skin nodules showing collagen necrosis. Similar nodules were found at autopsy in the periaortic tissues.

CASE 15.—F. H., female, aged 21 years, had had recurrent attacks of asthma since September, 1934. In spite of seasonal variations in her attacks corresponding to the pollinating periods, skin tests with pollens were found to be repeatedly negative. Associated with the asthmatic paroxysms were repeated migratory interstitial pulmonary infiltrations, sputum eosinophilia, marked polynucleosis, and blood eosinophilia up to 54 per cent. With each acute asthmatic episode there appeared electrocardiographic changes which, during some of the attacks, indicated abnormalities in the deflections and amplitudes of the P and T waves and, in others, of the QRS complexes as well, suggestive of myocardial involvement. These, however, proved to be reversible in character, returning to normal with the cessation of the asthmatic paroxysm. In the course of one of these attacks an acute pericarditis supervened (Fig. 5). During this episode the asthma subsided. With the termination of the pericardial manifestations, which were present for almost a month, the patient developed an attack of polyarthritis, lasting about a week. Following this, there was an exacerbation of her asthma which slowly yielded to symptomatic therapy. She was discharged, improved, Dec. 24, 1938, and readmitted in April, 1939. On this occasion there was a return of the pulmonary infiltration previously noted, and, in addition, enlargement of corresponding hilar and paratracheal lymph nodes, as well as right-sided pleural exudate. There was again evidence of abnormal electrocardiographic changes (Fig. 6). The P waves were high in Leads II and III. T_2 and T_3 were low. The high P waves in Leads II and III were interpreted as indicating hypertension of the lesser circulation. X-ray examination of the sinuses at this time still showed a bilateral antritis and ethmoiditis, especially on the right, and also involvement of the sphenoid sinus. Under symptomatic therapy the attacks subsided, and with their disappearance the pulmonary as well as the electrocardiographic changes returned to normal.

On her seventh admission, in April, 1940, a bilateral Caldwell-Luc operation was performed because of the marked purulent sinusitis. She had a stormy recovery and finally left the hospital improved. She was readmitted for the eighth time in September, 1940, with another attack of asthma. Thick pus was found in the ethmoids and sphenoids. Because of an extensive purulent nasal discharge, the elevation of the temperature to 104° F., and the presence of signs of meningeal irritation, a spheno-ethmoidectomy was done. Shortly thereafter, she developed an aputrid pulmonary abscess. During this period the asthma disappeared. Sulfathiazole was administered, and, after three weeks,

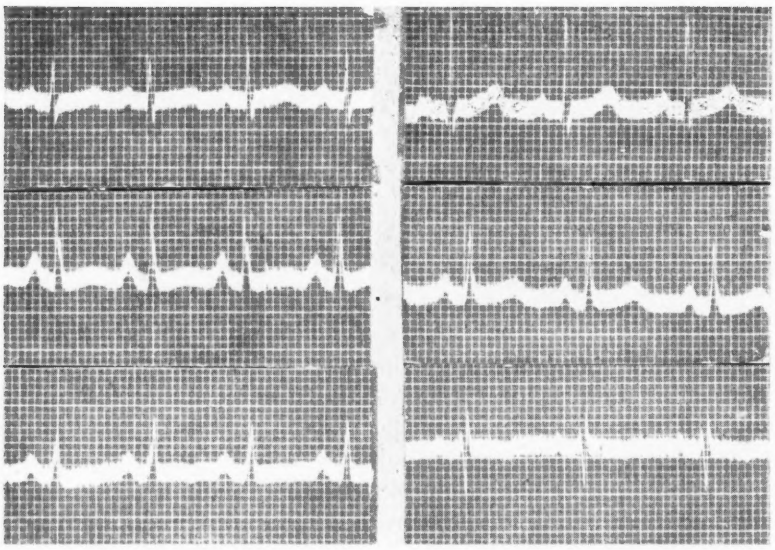

Fig. 6.—Case 15. *A*, Record taken April 11, 1939. Sinus tachycardia, rate 130. P wave high in Leads II and III, T_2 and T_3 low. *B*, June 2, 1939. Leads I and II normal. Q_3 present.

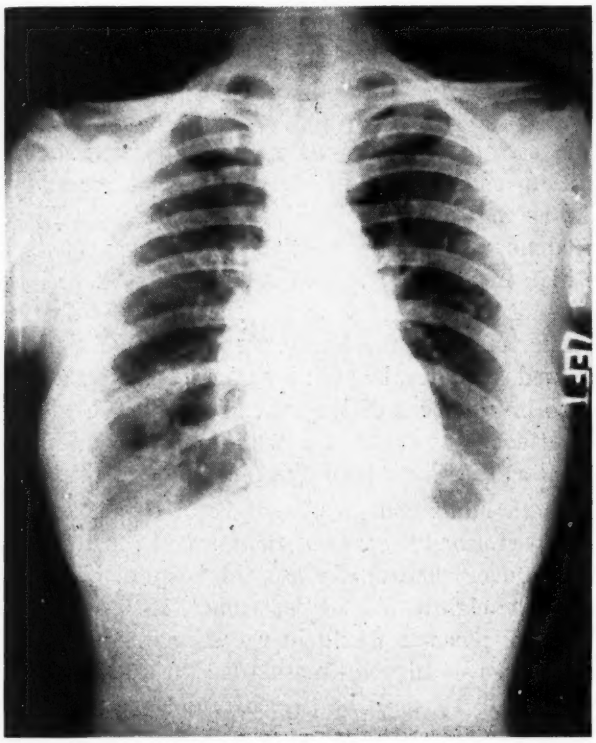

Fig. 7.—Case 15. Infiltrations in both lower lobes. Hilus lymph nodes enlarged.

the lung abscess gradually cleared up. She was well for several months until she entered the Montefiore Hospital in April, 1941, because of the development of arthritis associated with recurrent papular and urticarial skin eruptions. Biopsy of one of the papular nodules disclosed perivascular infiltrations with eosinophiles. The electrocardiogram, which had returned to normal after her discharge from the Mount Sinai Hospital in 1940, was still unchanged except for tachycardia. She left the Montefiore Hospital in July, 1941, slightly improved, only to re-enter the Mount Sinai Hospital on Sept. 5, 1941, because of the return of the joint pains.

She shuttled back and forth from home to the hospital and was discharged only to return for the eleventh time on April 23, 1942. During her tenth admission she ran an extremely stormy course characterized by edema of the larynx, bilateral pneumonia with effusion, questionable infarction of the liver, and questionable perirenal hemorrhage. Two weeks prior to the last admission she had been practically in status asthmaticus, requiring adrenalin every half hour.

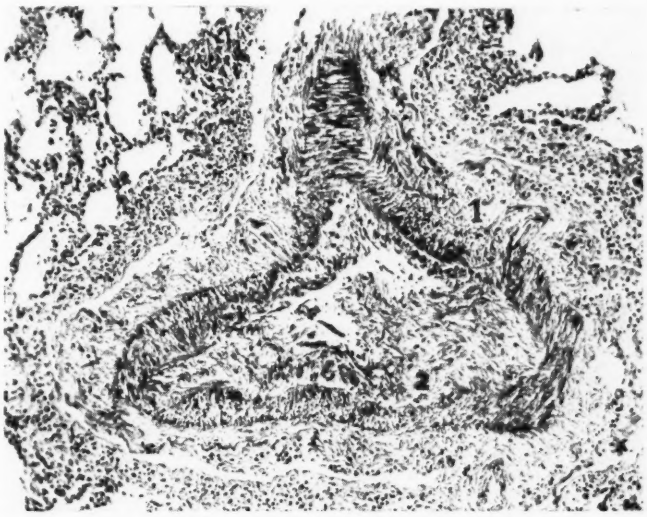

Fig. 8.—Case 15. Pulmonary artery showing: 1. Partial necrosis of vessel wall. 2. Conspicuous intima proliferation characteristic of endoarteritis obliterans.

Skin manifestations such as purpura and conglomerate hemorrhages prevailed. Abdominal symptoms, characterized by pain, distension, vomiting, and constipation, were severe. Headache and dimunition of vision were associated with temperature rise to 103° F. On this admission she was severely emaciated. Her face showed edema of the lids. The hands were puffy, the fingers painful and tender, covered with purpuric spots.

The liver and spleen were enlarged. The hemoglobin was 51 per cent, red blood cells 2,700,000. The white blood count was 19,250 with 8 per cent eosinophiles. The electrocardiogram during the last hos-

pitalization revealed tachycardia, QRS of low voltage, T_1, T_2, and T_3 low, T_4 inverted (Table I). The blood urea nitrogen was 10 mg. per cent, the sugar 110 mg., cholesterol 150 mg., and the ester was 60 mg. per 100 c.c. The total protein was 6.1 Gm. per 100 c.c., with a normal albumin-globulin ratio. The urine was essentially negative except for urobilin 1:640. Three days after admission the patient died.

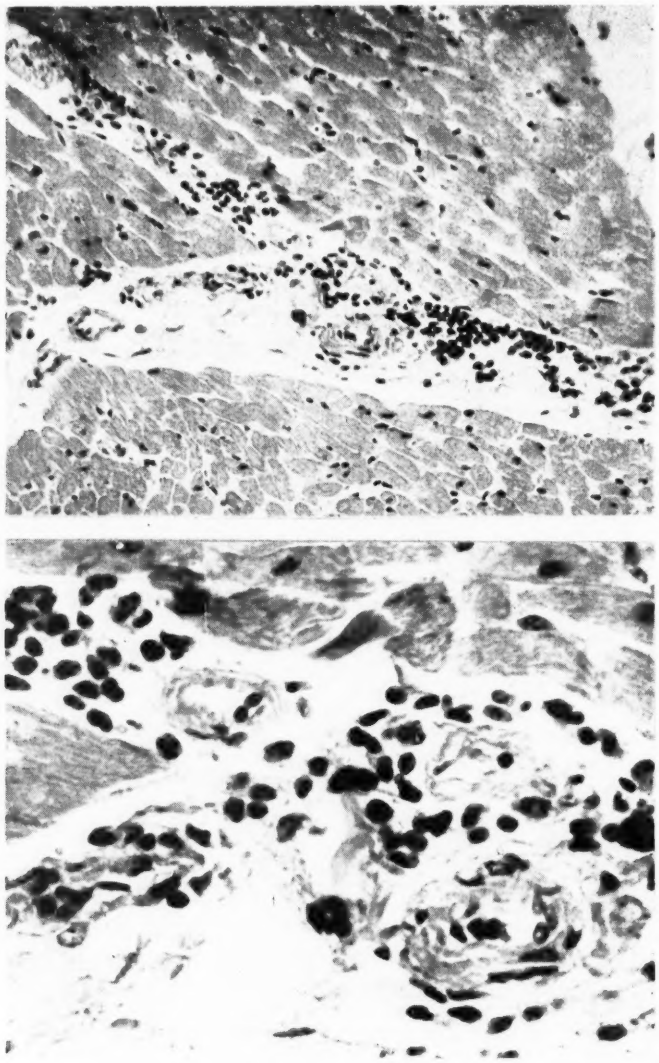

Fig. 9.—Case 15. Heart muscle. *A*, Low-power magnification; eosinophilic infiltration of myocardium. *B*, High-power magnification; (a) eosinophilia, (b) blood vessel.

Necropsy: Macroscopic Examination.—Dense bilateral pleuritis with encapsulated effusion, chronic bronchitis, and emphysema were in evidence. There was a residual cavity in the left upper lobe. Chronic inflammation of the endocardium and pericardium and dilatation of the

right atrium and both ventricles were present, as well as myofibrosis of the right ventricular posterior wall, and endocardial hemorrhages. The abdominal cavity disclosed localized fibrinopurulent peritonitis. The liver, spleen, and kidneys showed disseminated tubercles. The liver also showed chronic passive congestion. There was a generalized hyperplastic lymphadenopathy, with caseating periportal lymph nodes. Hemorrhagic lesions were present in the skin.

Microscopic Examination.—Lungs: Interalveolar septa were infiltrated by eosinophiles, and there was edema of the bronchial walls. The pulmonary blood vessels show endoarteritis obliterans (Fig. 8).

Heart: Diffuse infiltration of the cardiac muscle by eosinophiles was present (Fig. 9).

Intestines: There was a diffuse eosinophilic infiltration with severe ulcerative colitis of the ascending colon associated with endoarteritis obliterans.

Abdominal muscles disclosed diffuse eosinophilic infiltration.

Uterus: Vessels showed endoarteritis obliterans, necrotizing arteritis, and periarteritis (Fig. 10).

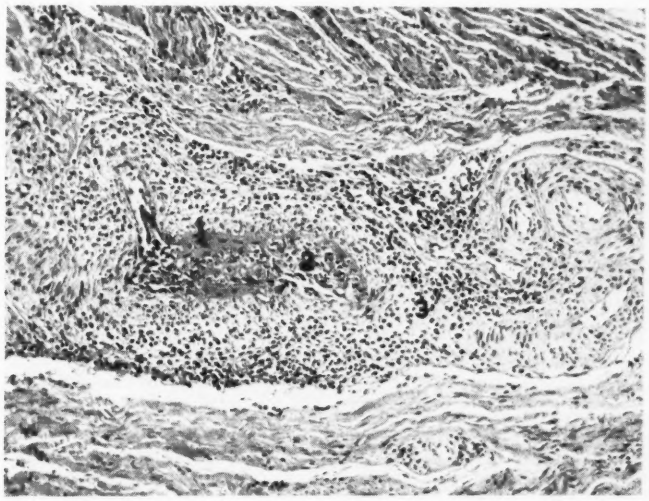

Fig. 10.—Case 15. Artery of the cervix of uterus showing: 1. Necrotizing arteritis. 2. Endoarteritis obliterans. 3. Periarteritis with conspicuous eosinophile cells.

Comment (by Dr. Paul Klemperer).—"Diagnosis: Diffuse vascular disease and obliterating endoarteritis of many organs. The outstanding feature in this case was the diffuse involvement of small and medium-sized arteries in various organs both of the greater and lesser circulation. The vessels showed a striking cellular proliferation of the intima whereby the lumen became markedly compromised. The thickened intima consisted of fibroblasts and was often vascularized and was mostly infiltrated by polynuclear leucocytes, many of which were of the eosinophilic variety. Perivascular cell infiltration was present but.

as a rule, moderate. There were, however, medium-sized vessels in the cervix of the uterus which showed, in addition to the endoarterial changes, a striking periarterial cellular infiltration and fibrinoid necrosis of the proliferated intimal connective tissue. Only this was reminiscent of periarteritis nodosa.

"Necrotic areas in spleen and liver were tuberculous on histologic examination and were so diagnosed although no tubercle bacilli were found, even after guinea pig inoculation."

CASE 16.—K. W., aged 35 years, was admitted to the Mount Sinai Hospital, July 13, 1941. He gave a negative family history for allergic diseases. At the age of 21 years he developed urticaria, at 22 years, hay fever. In 1931 he had an appendectomy because of recurrent abdominal cramps. In 1935 he developed asthma which gradually became severe, requiring repeated injections of adrenalin. In 1938 he went to California for relief of the asthma and, while there, developed episodes of watery diarrhea and cramps which became worse after meals. In 1940 he was hospitalized at the Huntington Hospital at Pasadena, California, for asthma, diarrhea, and hip pain. At that time a blood examination disclosed a white blood cell count varying between 37,000 and 70,000; with 65 to 82 per cent eosinophiles. The urine and other laboratory examinations were negative. The blood culture was negative. The blood pressure was 110/80. X-ray examination of the chest showed an old pleurisy at right base posterior. Sinus x-ray disclosed pansinusitis. Because of the marked eosinophilia, a biopsy of the muscle of the leg was made, with negative results.

The patient returned to New York in 1941 and was hospitalized at the Newark Hospital because of pain in the back, diarrhea, asthma, and loss of weight. On admission, the significant findings in addition to asthma were a faint systolic murmur at the apex of the heart. The spleen and liver were not enlarged. X-ray examination of the gastrointestinal tract showed canalization of the second portion of the duodenum; the colon was negative. An exploratory laparotomy was done, some adhesions were cut, and the gall bladder was removed. Following the operation he felt well and temporarily became free of asthma and diarrhea. The blood count returned to normal. He remained well and continued to gain weight until four months before admission to the Mount Sinai Hospital, when his asthma reappeared. The diarrhea and abdominal cramps also returned. His abdomen and legs became progressively swollen, and he developed anorexia and vomiting. Purpura appeared on his skin.

On examination of the lungs, typical sonorous râles characteristic of asthma were audible. The heart was not enlarged. Tachycardia and a soft systolic murmur were heard at the apex. The liver was four fingerbreadths below the costal margin. The abdomen and the ankles were swollen. The hemoglobin was 80 per cent. The red blood cells

4,020,000, white blood cells 16,500; polynuclear cells 85 per cent; lymphocytes 18 per cent; mononuclear cells 18 per cent. There were no eosinophiles present. The urine was negative. The blood urea was 24 to 60 mg. per cent; the total protein was 8.1 Gm.; the albumin 3.8; the globulin 4.8 Gm. The blood pressure was 100/70. The venous pressure was 13 cm. of water; the circulation time with the saccharin method was 28 seconds; the ether time was 14 seconds. The electrocardiogram showed QRS slurred of low voltage, T_1 isoelectric, T_2 and T_3 low, T_4 inverted, RT_4 depressed, evidence of intraventricular block. The x-ray examination of the lungs showed infiltration throughout both lower lobes, but more on the right where pleural thickening was found. The heart was not enlarged.

While under observation, the chief symptoms consisted of fever, tachycardia, and ascites. Bilateral pleural effusions, transudative in character, were also present. On one occasion, the cytological examination of the pleural fluid showed 5 per cent eosinophilia. He was digitalized but signs of cardiac failure persisted in the absence of enlargement of the heart. Cardiac arrhythmia supervened, and auricular flutter was, on one occasion, demonstrable clinically and in the electrocardiogram. After he had been in the ward for three weeks he went into cardiac failure and died.

Necropsy: Macroscopic Examination.—Lungs showed multiple pulmonary infarctions, pulmonary congestion, atelectasis, and emphysema, with embolization of the apical artery of the right upper lobe. Bilateral pleural effusion was present. The right side yielded 2,000 c.c. bloody fluid, and the left, 1,000 c.c. serous fluid. There was a chronic adhesive pericarditis. Mural thrombi of the right auricle and left ventricle appeared, with thrombophlebitis and ascending thrombosis of the inferior vena cava with partial occlusion of the right renal vein. Chronic passive congestion of the liver and of the viscera were present. There were acute erosions of the esophagus. The small and large intestine were greatly congested and, in places, deeply reddened. There were adhesions to the gall bladder bed. Focal areas of kidney atrophy were present.

Microscopic Examination.—Lungs: There were multiple infarctions in all stages of development, due to emboli.

Heart: There was extensive fibrosis throughout all the sections with striking vascular changes, characterized by thickening of small and medium-sized arteries. A fibrosing pericarditis was present. Inferior vena cava showed chronic endophlebitis with acute thrombosis.

Liver: The lobular architecture was accentuated because the centers of the lobules were exceedingly congested with atrophy. In several sections, medium-sized arteries were found with thickened walls, fibrous replacement of media, and destruction of elastic membrane. Peculiar hyalinization occurred within these severely altered vessels.

Spleen: The significant pathology resided within the arterioles which had thickened walls due to a periarteriolar fibrosis and, often, a narrowed lumen.

Adrenal: Striking arterial changes appeared within the periadrenal fat tissue which was completely fibrosed and capillarized.

Kidneys: There were superficial cortical scars with atrophic tubules, and several arteries with fibrous walls.

Gastrointestinal tract: The pylorus disclosed a serosa which was thickened and infiltrated with lymphocytes. There was also present a recanalized vessel with perivascular fibrosis.

Comment (by Dr. Paul Klemperer).—"This was a case characterized by a diffuse disease of the medium-sized arteries in many organs. The arterial involvement had led to a destruction, more or less advanced, of the media and adventitia, with fibrous replacement. The intima was proliferated. These vascular lesions were responsible for the changes in various organs, especially fibrosis of the myocardium. The exact nature of the arterial process cannot be ascertained because the lesions were healed in an anatomic sense. It is probable, however, that the destruction of the arterial walls was preceded by an arteritis. The fibrosing pericarditis, as well as the fibrosing lesions of the retroperitoneal tissue, was of great significance in the clinical picture. One is inclined to think, in this case, of a morbid process affecting the collagen tissue. Of course, the obvious diagnosis suggested by this widespread involvement of the vessels, such as rheumatic fever or periarteritis nodosa, cannot be made."

SUMMARY OF FINDINGS

A summary of the histopathologic findings in the most important organs of these cases is as follows:

Pulmonary Lesions.—The fugitive pulmonary infiltrations as revealed by x-ray examination, referred to by some as "Löffler's[2] pneumonia, were found to be due to congestion, edema, and thrombi in small vessels, in Case 13, and infiltration of the interalveolar septa with eosinophiles, polynuclear and lymphocytic cells, plus edema, in Cases 14 and 15. The eosinophilic inflammatory involvement of the bronchial tubes, with edema and hyalinization of the basement membrane characteristic of bronchial asthma, was also seen. In addition, atelectasis and emphysema, varying in extent depending on the duration of the asthma, were present. In Case 16, the most significant findings were pulmonary congestion and areas of infarction, indicative of the terminal events in the underlying vascular disease. The most significant pathologic lesion in the lungs was the degree of the hyperergic reaction in the pulmonary vessels. This varied from the simple thickening of small vessels involving the intima, in Case 13, to acute necrotizing arteritis with periarterial eosinophilic infiltrations, in Case 14, and endoarteritis obliterans, in Case 15. In the pleura the hyperergic re-

sponse was characterized by sclerosis of small vessels and inflammatory exudate with eosinophiles.

Pericardial and Cardiac Manifestation.—The pericardium showed acute and chronic inflammatory alterations with eosinophilic infiltrations, sclerosis of small vessels, and diffuse fibrosis.

The heart showed chronic inflammation of the endocardium and myocardium. The myocardium in Case 13 disclosed arteritis with perivascular fibrosis, and diffuse inflammation with eosinophilic exudate superimposed on chronic granulation tissue; in Case 14 there were vessel changes characteristic of periarteritis nodosa, atrophy and degeneration of muscle fibers, areas of necrosis and giant cell reaction; in Case 15 there were areas of myofibrosis, diffuse infiltration of the cardiac muscle by *eosinophiles;* and, in Case 16, there was noted diffuse fibrosis of the myocardium and periarteriolar fibrosis. Endophlebitis and acute thrombosis of the inferior vena cava were additional findings in this case.

Abdominal Organs.—The liver exhibited amyloidosis and vessel changes in the nature of healed periarteritis nodosa in Case 13, vessel changes signifying periarteritis nodosa in Case 14, passive congestion and disseminated granulomatous areas indistinguishable from tubercles in Case 15 although no tubercle bacilli were found either on section or guinea pig inoculation, and arterial thickening with fibrous replacement of the media and destruction of the elastic membrane in Case 16.

The gastrointestinal tract in Case 15 showed endoarteritis obliterans probably responsible for the ulcerative colitis which this patient had during life. In Case 16 the small and large intestines were congested and the pylorus disclosed a serousa thickened and infiltrated with lymphocytes, and a recanalized vessel with perivascular fibrosis.

The kidneys in Case 13 presented amyloidosis, in Case 14 there were vessel changes indicative of periarteritis nodosa, in Case 15 disseminated tubercles similar to those found in the liver and spleen, and in Case 16 arterial fibrosis. It is significant that only in Case 15 did the kidneys participate actively in the clinical course, being responsible for the hypertension and uremia.

The medium-sized vessels in the cervix of the uterus in Case 15 in addition to endoarterial changes showed striking periarterial infiltration with fibrinoid necrosis of the proliferated intimal connective tissue (Fig. 10).

COMMENT

The importance of the vascular reactions in the symptomatology of the aforementioned cases is obvious. The fact that all of the patients in this group were asthmatics implies that we were dealing with allergic individuals who, by their very nature, tended to respond in a hyperergic manner to antigenic excitants. The existence of polyvalent sensitivity, the variations in the degree of the hyperergic vascular reaction involving arteries and veins, together with the characteristic pres-

ence of fibrinoid necrosis of collagen connective tissue, seen in biopsy sections in some of our cases, although not limited to hyperergic reactions, fit into the concept of the pathogenesis of hypersensitiveness.

Polyvalent sensitization was evidenced in the multiplicity of the exciting agents of bacterial and nonbacterial origin which, in at least seven of the cases, acted synergistically in precipitating the asthma syndrome. The sinuses were the only known foci of infection, yielding a variety of bacterial flora on culture. The microorganisms recovered from the sinus washings and bronchial secretions differed, not infrequently, in the same individual with each new paroxysm.

The positive skin reactions elicited by various polysaccharides of the pneumococci, corresponding to the pneumococci recovered from the sinuses and bronchial secretions in Cases 5, 7, 14, and 15 (Table I), coupled with the systemic reactions indicate a possible sensitization to these organisms. It should be pointed out, however, since the tests were not made with the carbohydrate fractions of autogenous bacteria, no claim as to specificity is made. The subcutaneous injection of autogenous vaccines composed of various bacteria derived from sinus washings, succeeded repeatedly by symptoms of asthma in Case 10, and, in Case 14, by pulmonary infiltrations, petechiae, and cutaneous ecchymoses indicative of hyperergic vascular response, is also suggestive of bacterial hypersensitiveness. Whereas this sequence of events seems to point to a certain relationship, possibly only incidental, between the bacterial products employed in the injections and the systemic reactions elicited in the cases under discussion, such reactions may be either of a broad specificity involving some common antigenic component present in a variety of bacterial organisms, or nonspecific and based on some other undetermined mechanism of hyperreactivity. When dealing with bacterial allergy, in contrast to simple controllable nonbacterial protein hypersensitiveness, characteristic symptoms of the disease to which the patient is subject may be reactivated not only by contact with homologous bacteria responsible for the initial sensitizing effect, but possibly also by viruses; and, in the light of Shwartzman's observations, by heterologous bacteria and their toxins as well as by antigen-antibody complexes of nonbacterial origin. Such nonspecific effects explain why every fresh "cold" or infection of the respiratory tract in patients with chronic sinal disease, or even in those whose sinuses have been previously operated on, may be followed not only by recrudescence of asthma but by symptoms in other shock tissues present in the patient such as the heart, pericardium, and pleura, subject to the same allergenic excitants. The only positive conclusion, therefore, that may be drawn from the above findings is that, during *some* asthmatic attacks, a current allergenic relationship between the bacteria recovered from an active focus of infection and the presenting symptoms may be demonstrable. This may be accomplished either by means of positive skin tests with suitable specific carbohydrate fractions or by the method of

parenteral injections of autogenous vaccines provided they are succeeded by the production of the disease complex in question. This may be regarded as an indication of bacterial allergy; it does not necessarily imply specificity, and it does not follow that subsequent attacks would be due to the same microorganisms.

The diversity both in distribution and degree of the vascular response was manifest in the autopsied cases in the number of different organs affected and variations in the vessel changes. These ran the gamut from simple arterial thickening to perivascular eosinophilic infiltrations, necrotizing arteritis, periarteritis nodosa, endoarteritis obliterans, and fibrosis of small and medium-sized arteries. The latter represented the end results of a preceding arteritis. Involvement of the veins was characterized by endophlebitis of the inferior vena cava in Case 16, resulting in a superimposed thrombosis. It should be noted that vessels in various states of reactivity were present not only in different tissues in the same patient, but also in the same organ. This was exemplified in the cervix of the uterus in Case 14, where the medium-sized arteries showed endoarterial changes with marked periarterial eosinophilic infiltrations, as well as fibrinoid necrosis of the proliferated intimal connective tissue. Whereas the perivascular eosinophilic infiltration, the necrotizing arteritis, and periarteritis nodosa may be said to represent the hyperergic or exudative stages, the endoarteritis obliterans and fibrosis of small and medium-sized arteries, inasmuch as they are no longer reversible, may be designated as belonging to the anergic phase. Depending on the state of anergy, the eosinophilia may completely disappear from the blood and tissues, as found in Case 16.

The simultaneous precipitation of both the asthma and the polymorphous vascular reactions in these cases by the same allergenic stimulation lends support to the concept that bronchial asthma is fundamentally an expression of a hyperergic vascular response, and that the accompanying vessel changes do not represent disease entities but rather qualitative and quantitative degrees of hyperergic and anergic reactions.

Similar findings have been described by Klinge,[3] and Gruber,[4] in their experimentally induced hyperergic vascular reactions following bacterial and serum sensitization. Clark and Kaplan[5] found, in patients dying four and nineteen days after serum sickness, "necrotizing arteritis and periarteritis of the small coronary vessels" in addition to histologic changes in the mural and valvular endocardium as well as in the aorta and pulmonary vessels. Rich[6] recently described lesions in the viscera characteristic of periarteritis nodosa in five patients who, shortly before death following therapeutic injection of foreign serum, had developed hypersensitive reactions. Four of these patients had received sulfonamides, but in at least two of those cases there was evidence that the hypersensitive reaction was that of serum sickness and not due to drug sensitization. In one patient who had received sul-

fathiazole as a prophylactic measure against aspiration pneumonia and in whom no infection appeared at autopsy, vessel changes indicative of periarteritis nodosa also appeared, in addition to widespread visceral, focal, inflammatory necrotic lesions described by Lederer and Rosenblatt.[7] That the sulfonamides may likewise be responsible for myocarditis characterized by infiltration of mononuclear and polymorphonuclear leucocytes including eosinophiles has been reported by French and Weller.[8] Thus, it seems that these drugs behave in a manner similar to serum sensitization.

In the light of the foregoing evidence favoring the view that the vascular reaction is a fundamental response to allergenic stimulation, it may be permissible to formulate a working hypothesis dealing with the effects of these reactions in different types of bronchial asthma and the heart.

Based on general experience, it may be assumed that in the average allergic individual sensitive to foreign substances who develops bronchial asthma, the bronchi serve as the major shock organ. The underlying lesion probably consists of increased permeability of the bronchial vessels and edema, which latter is usually noted in autopsy sections. Here both the lungs and heart are normal.

In the patient subject to polyvalent sensitivity in whom bacterial infection plays a prominent sensitizing role, repeated attacks of asthma mediated by a similar mechanism may be accompanied by bouts of bronchopneumonia, which, in turn, may be followed by chronic bronchitis and obstructive emphysema. This may lead to hypertension of the lesser circulation, sclerosis of the pulmonary vessels, and right-sided cardiac hypertrophy with electrocardiographic changes, as previously described by us,[9] leading to ultimate cardiac failure. This is a type of cardiac complication more or less due to mechanical interference within the lesser circulation.

In the more highly sensitive case with multiple shock tissues, where diffuse hyperergic responses occur, not only the vessels of the bronchi but also those of the pulmonary parenchyma as well as of many other tissues may become affected as above indicated. In the early phases, these vascular reactions in the lung demonstrable by x-ray examination as fugitive pulmonary infiltrations, so-called Löffler's pneumonia, may be reversible. With repeated attacks and the resulting chronic allergic inflammatory involvement of the interalveolar septa, fibrosis and destruction of the vessels of the alveolar walls may ensue and emphysema supervene. This was evident in the lungs of the autopsied Cases 13, 14, and 15.

The concurrent development of the hyperergic vascular reaction in the heart gives rise to electrocardiographic abnormalities which may be reversible in the early stages, but ultimately, depending upon the extent of damage sustained by the myocardium, irreversible. This was illustrated in the course of Case 15 observed from 1934 to 1942. The

reversible changes may be due possibly to spasm of capillaries and edema associated with an inflammatory exudate characterized by interstitial infiltration of the myocardium with eosinophiles similar to that seen in Case 15, and also recently reported in a fatal case by Chafe, et al.[10] That vessel spasms and edema do occur in animals in the course of sensitization had been clearly shown by Abel, et al.,[11] who studied microscopically the reaction of peripheral vessels to histamine and anaphylaxis in the living rabbit. Wilcox and Andrus[12] were also able to demonstrate, by means of direct leads from the isolated perfused hearts of guinea pigs sensitized to horse serum, various electrocardiographic abnormalities usually associated with mechanical constriction of the coronary arteries, on exposure to small amounts of homologous antigen. The deviations consisted of acceleration of the heart rate and alteration in the amplitude of contraction. The PR interval was prolonged, and there were changes in the form of the QRS and T complexes, as well as ectopic rhythms. They were also able to establish that these changes were due to actual alterations in caliber of the coronary vascular system and not to an increase in heart rate or muscle tonus. It is conceivable that, if the hyperergic vascular reactions in the myocardium are slight, the resulting local anoxemia leading to focal myofibrosis may be insufficiently large to affect the electrocardiogram permanently. This was illustrated in various stages of the clinical course in Case 15. Repeated or prolonged antigenic stimulation, however, may lead to thickening of small arteries, arteritis, periarteritis, and perivascular fibrosis, with generalized fibrosis of the myocardium and endocardium as seen in the histologic sections of the hearts of Patients 13, 14, 15, and 16 in this group, giving rise to irreversible changes in the electrocardiogram. This series of events, therefore, is responsible for another type of cardiac involvement in bronchial asthma. Thus, it may be seen that the heart in asthma may be completely normal, it may be hypertrophied and insufficient as a result of increased tension of the lesser circulation, or it may be directly involved as part of the generalized hyperergic vascular response.

With the participation of the vessels of the serous membranes in the hyperergic reaction, clinical syndromes such as constrictive pericarditis or polyserositis may follow. The involvement of the kidney gives rise to so-called hypertensive renal disease. Lesions in the liver, or gastrointestinal tract (Cases 13, 15, and 16), may be responsible for a variety of symptoms referable to the disturbed function in these tissues, including ulcerative colitis noted in Case 15.

While such extensive vascular involvement may result in irreversible changes in vital organs leading to a fatal issue, as in the cases under discussion, it should be emphasized that there is a large category of patients, nine cases in this series, who present similar hyperergic responses and electrocardiographic changes but in whom the pathologic process is reversible and fortunately limited to two or three organs, such as the

sinuses, lungs, and heart. These individuals may be distinguished from the usual run of simple cases of bronchial asthma by a characteristically high blood eosinophilia, fugitive pulmonary infiltrations, and electrocardiographic changes. Such cases may be regarded as larval or formes frustes of diffuse hyperergic vascular disease. Here, early diagnosis and individualized therapy directed to the elimination of sources of infection, possibly by radical sinus operation in the early stages of the disease in some instances, change of climate, immunization, and removal of offending agents, may bring about a reversibility in the hyperergic response, and arrest in the progress of the disease. This was achieved in eight of the patients of this group.

SUMMARY

This report deals with fifteen cases suffering from typical bronchial asthma and one in which bronchospasm and cough were the presenting symptoms. Four of the asthmatic patients died and were available for necropsy studies. The chief precipitating factor was considered to be bacterial allergy resulting from chronic sinal infection. In seven of the sixteen cases, pollen and food hypersensitiveness played additional exciting roles.

The major attacks of asthma were accompanied by inflammatory interstitial lesions in the lungs, sputum eosinophilia, and reactions in serous membranes, characterized by pleural effusions in eight cases, peritoneal exudates in four, and pericardial involvement in three cases. The aspirated fluids were sterile and the eosinophile content ranged up to 100 per cent.

Coincidentally with the asthmatic attacks and serous membrane reactions, there appeared electrocardiographic abnormalities in the deflections and amplitudes of the P waves and the QRS complexes. These returned to normal with the termination of the asthmatic attacks in twelve of the cases and were irreversible in the four who died.

Increase in blood eosinophilia in all cases, ranging at times to 84 per cent, as well as augmentation of the eosinophile granulocytes in the bone marrow were outstanding features.

Recurrent skin lesions were characterized by urticaria, angioneurotic edema, purpura, and hemorrhagic necrosis in one case.

Biopsies of the cutaneous lesions, including a subcutaneous nodule from Case 13, disclosed perivascular infiltrations with eosinophilia, collagen necrosis, as well as periarteritis nodosa observed in sections of the subcutaneous nodule.

The chief pathologic changes responsible for the clinical manifestations in the four cases that came to autopsy were found to be due to varying degrees of hyperergic and anergic vascular reactions in the lungs, the myocardium, serous membranes, etc. These reactions were characterized by thickening of the intima of small vessels, necrotizing arteritis, endoarteritis obliterans, and fibrosing arteritis.

CONCLUSIONS

1. The simultaneous precipitation of both the asthma and the polymorphous vascular reactions in these cases by the same allergenic stimulation lends support to the concepts (a) that bronchial asthma is fundamentally an expression of hyperergic vascular response which may be reversible or irreversible, and (b) that the accompanying resultant pathologic vessel changes do not represent disease entities but rather qualitative and quantitative degrees of hyperergic and anergic responses.

2. The syndromes dependent on such vascular reactions in the myocardium, pericardium, and other serous membranes, expressed as cardiac insufficiency, constrictive pericarditis, or polyserositis, may therefore be attributed to an allergic mechanism.

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STUDIES ON HYPERSENSITIVITY DUE TO SUBSTANCES EMPLOYED IN THE FUR INDUSTRY

I. The Significance of Cutaneous Reactions to Fur Dye Dust Extracts

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IT IS the purpose of this article and those to be reported later to crystallize in definitive form the amorphous impressions and speculations relative to the etiology and acquisition of allergic syndromes in the fur industry. We have had the opportunity to investigate, to attempt specific diagnosis, and to treat many patients in the fur industry. Only too often the careful search into history, the comprehensive survey of occupational and extraoccupational environment, the patient pursuit of all clues, relevant or apparently irrelevant, have resulted in a clinical conviction of causal relationship between suspected substance and symptom complex without possibility of specific proof. This possibility was denied because of the present state of our knowledge of certain aspects of the phenomenon of hypersensitiveness.

We and many others working within the fur industry have the impression that the percentage of allergic manifestations is much higher in the persons in this occupational group than in the general population. This in itself, if true, is extremely provocative, especially when it is realized that this particular environment is replete with nonprotein, inorganic, often toxic substances, as well as common and uncommon recognized allergens. The implication that hypersensitivity is acquired after prolonged contact with the above substances is obvious. That atopic individuals manifest their first allergic symptoms on entering the industry is undoubtedly true, but it is unreasonable to suppose that the industry draws to itself an unusually high percentage of atopic individuals. The acquisition of sensitivity to nonprotein and inorganic substances is the point in question and remains the clinical impression.

To prove this, not only must a causal relationship between these substances and symptomatology be shown, but also antigenicity, actual or anomalous, of these substances. To affirm or deny this hypothesis is the purpose of our projected investigations. That this be accomplished is of importance not only from the viewpoint of knowledge and the benefits that accrue therefrom, but also from the viewpoint of practical application. Industrial health insurance prevails and compensation laws demand specificity in tendered causal relation between suspected substances and symptoms.

In investigating cases of ophthalmic, nasal, bronchial, and dermal allergy from the fur industry, an intracutaneous test is routinely made with an extract of autogenous shop dust. The rationale of this procedure is at once apparent and logical. If the reaction is suggestively positive, even in the presence of multivalent sensitivity to substances outside the industry, the tendency is immediately to propound a causal relationship. Undoubtedly, in many instances this is justified, but there are more instances in which it is not. The theoretically possible antigenic substances in this occupational environment are protean in structure and little understood in their relation to hypersensitiveness. Because of this, an a priori attitude is maintained toward them and the presenting symptomatology; namely, the patient is a worker in the fur industry and therefore derives his asthma, vasomotor rhinitis, and conjunctivitis from it. This attitude is markedly enhanced by the presence of a positive cutaneous reaction to the autogenous shop dust or a positive paraphenylene diamine patch test.

To determine the actual specificity of such cutaneous reactions and to ascertain their significance relative to occurrence of allergic manifestations in this occupational group, we prepared a stock shop dust extract and intracutaneously tested 100 allergic individuals within and without the fur industry.

The extract was prepared from the sieved sweepings of numerous shops engaged in the dyeing, blending, and manufacture of fur apparel. The accepted procedure was followed; that is, defatting with ether, extracting with a protein leach, Seitz filtering, and culturing for sterility. Since the sweepings represented a conglomerate of animal hairs and dander, wood dusts, tanning agents, dyes, paraphenylene diamine, their alteration products, and the usual decomposition products of a physical environment, the extract was labelled F. D. D.

The patients upon whom tests were performed were chosen from the City Hospital Allergy Clinic, from our offices and from a group of individuals with cases prepared for compensation debate. They fell into two distinct groups: Group A, representing those allergic patients not associated with the fur industry and Group B, representing those allergic patients associated with the fur industry. The latter group was further differentiated into two subdivisions: (1) those in whom symptoms were suspected to be occupational, and (2) those in whom symptoms were not suspected to be occupational.

The necessary diagnostic procedures were carried out on all of these patients, including the full complement of commonly employed skin tests; in addition, an intradermal test with fur dye dust extract was made and, wherever thought necessary (Group B-1), patch tests with 2 per cent paraphenylene diamine, the oxidation products of the latter (quinone di-imine), and inhalation tests with extracts of suspected substances. In Table III are shown the results of these tests and analyses in Group B-1.

As a control group, five nonallergic individuals were used. Each was intracutaneously tested with stock house dust (H. D.), and fur dye dust extracts. All gave negative to slight positive reactions. This group and results of testing is not included in Table I.

TABLE I

SUMMARY OF CASES OF PATIENTS TESTED WITH STOCK HOUSE DUST AND FUR DYE DUST EXTRACTS

	NUMBER OF PATIENTS	% OF TOTAL	REACTION TO BOTH EXTRACTS	
			H. D.	F. D. D.
Group A	28	35	Pos.	Pos.
	18	22.5	Pos.	Neg.
	34	42.5	Neg.	Neg.
Group B	3	30	Pos.	Pos.
1	1	10	Pos.	Neg.
	6	60	Neg.	Neg.
	4	40	Pos.	Pos.
2	1	10	Pos.	Neg.
	5	50	Neg.	Neg.

Usual criteria for immediate positive reactions employed were erythema, enlargement of wheal with or without pseudopodia, itching. Reactions of 2 plus or greater were called positive.

Group A, Allergic patients not associated with fur industry. Group B, Allergic patients associated with fur industry:
1, Causal relation between symptoms, and occupational environment suspected.
2, Causal relation not suspected.

Table I represents an analysis of 100 allergic patients within and without the fur industry intradermally tested with extracts of both stock house dust and fur dye dust. Several interesting facts can be noted in this table. In each group in terms of percentage, the positive reactions to fur dye dust is approximately the same; that is, varying between 30 and 40 per cent. The positive reactions to house dust in each group is approximately the same, varying between 40 and 57.5 per cent. All patients, regardless into which group they fell, showed a positive reaction to house dust when there was a positive reaction to fur dye dust. There were patients with a positive reaction to house dust and a negative reaction to fur dye dust. There were others negative to both house dust and fur dye dust. There was *none positive to fur dye dust and negative to house dust.*

It can be seen clearly, then, that patients with no history of direct contact with fur dye dust often show a skin sensitivity to its extract. Conversely, patients with a history of prolonged contact may and do show absence of skin sensitivity to its extract. It is apparent that skin sensitivity to fur dye extract does not depend upon evident contact and that, in this regard, it acts in a manner similar to other atopens. Furthermore, since all patients who showed positive skin reactions to fur dye dust also showed positive skin reactions to house dust, and since there was no patient who showed a positive reaction to fur dye dust and a negative reaction to house dust, it is reasonable to hypothesize that both

dusts are in some manner constitutionally related. However, because there were patients who showed a positive reaction to house dust and a negative one to fur dye dust, it is also reasonable to assume that there is an essential constitutional difference between house dust and fur dye dust. This difference may be qualitative or quantitative. However, knowing the source of, and the probable composition of, the sweepings from which fur dye dust extract is prepared, we feel that this difference is most likely qualitative.

An additional point can be made concerning the possible structure of the antigenic fraction or fractions of fur dye dust from the observation that the dermal reaction is of the immediate variety, entirely similar to the reaction produced in the skin of sensitive patients by other atopens. From this it may be deduced that this antigenic fraction or fractions resemble the structure of the antigen fractions of other common allergens.

The distribution of positive skin reactions to fur dye dust relative to both occupation and type of allergic manifestation is presented in Table II.

TABLE II

REACTION TO FUR DYE DUST IN VARIOUS TYPES OF ALLERGIC MANIFESTATIONS WITHIN AND WITHOUT THE FUR INDUSTRY

ALLERGIC SYNDROME	GROUP A	NUMBER POSITIVE	PERCENTAGE	GROUP B-1	NUMBER POSITIVE	PERCENTAGE	GROUP B-2	NUMBER POSITIVE	PERCENTAGE
Hay fever	30	10	30	0	–	–	7	4	57.14
Bronchial asthma	23	9	39.13	5	3	60	1	0	–
Allergic rhinitis	10	3	33.33	2	0	–	1	0	–
Contact dermatitis	0	–	–	2	0	–	0	–	–
Combined allergies	17	6	35.29	1	0	–	1	0	–
Total per group	80	28	35	10	3	33.33	10	4	40

From Table II it can be seen that in individuals in Group A, without history of contact, and in those in Group B-2, with history of contact but no reasonable suspicion of occupational environment as causative agent, positive skin reactions to fur dye dust occurred in a wide variety of allergic manifestations. In those in Group A especially is it to be noted that positive skin reactions to fur dye dust were distributed much in the same manner as skin reactions to other atopens, and that it was necessary to interpret them in relation to presenting symptoms in the same way; that is, as an indication of past, present, or future clinical sensitivity. Here, it was most often discovered on minute questioning that contact with fur dye dust was never made, and if made, was in such a circuitous route and for such infinitesimal periods of time that it was impossible to place any significance on it. In the individuals in Group B-2 the positive fur dye dust skin reactions appeared in cases of pollinosis with manifestations of hay fever. The implication of these

reactions could be no different from those in the individuals in Group A and certainly of no significance in relation to the presenting complaint.

In the individuals in Group B-1, however, where the occupational environment was suspected, evaluation of the positive fur dye dust skin reactions required further investigation. All of the patients in this group were tested by inhalation with the fur dye dust, by inhalation of aniline dyes, by patch with 2 per cent paraphenylene diamine (P. P. D.), and oxidized paraphenylene diamine or oxidized aniline dye. The patch tests and the inhalation of aniline dyes were attempted because these substances are commonly employed as fur dyes and dye bases. The oxidized paraphenylene diamine and aniline dye were used because, as has been pointed out by others,[1] the offending substance often is the alteration or oxidation (dehydrogenation) product of paraphenylene diamine or aniline dye rather than paraphenylene diamine or aniline dye itself.

TABLE III

EVALUATION OF FUR DYE DUST POSITIVE SKIN REACTIONS IN GROUP B-1 (OCCUPATIONAL CONTACT SUSPECTED)

MANIFESTATIONS	NUMBER OF CASES	STRONG POSITIVE REACTIONS TO			
		F. D. D.	PATCH TESTS		INHALATION TEST
			P. P. D.	2% ANILINE DYE OXIDIZED	ANILINE DYE
Hay fever	–	–	–	–	–
Bronchial asthma	5	3	0	1	1
Allergic rhinitis	2	0	0	0	0
Contact dermatitis	2	0	1	2	1
Combined allergies	1	0	1	1	0
Total	10	3	2	4	2

Inhalation of fur dye dust reproduced symptoms in none of the patients with positive fur dye dust skin reactions nor in the others with nasal or bronchial allergy. It was believed, however, that since aniline dye is a known fraction of the fur shop sweepings, inhalation tests with this might prove positive in those individuals with fur dye dust skin positive reactions. From the Table III it can be seen that this was decidedly not the case. Of the three patients with positive skin reactions to fur dye dust, only one gave a positive inhalation test. This same patient showed a positive patch test with oxidized aniline dye. Of the four patients who showed positive patch tests to oxidized aniline dye, only one gave a positive skin reaction to fur dye dust. The reactions of these four patients are recorded in Table IV.

TABLE IV

NUMBER OF PATIENTS	H. D.	F. D. D.	P. P. D. PATCH	INHALATION OF ANILINE
1	Pos.	Pos.	Neg.	Pos.
1	Neg.	Neg.	Pos.	Neg.
1	Neg.	Neg.	Pos.	Pos.
1	Neg.	Neg.	Neg.	Neg.

That the inhalation test was positive in one individual with positive skin reaction to fur dye dust and in one with negative skin reaction to fur dye dust, and that two individuals with positive fur dye dust skin reactions showed negative reactions on the inhalation test points to the lack of relationship between the aniline dye and the antigenic fraction or fractions in fur dye dust. Referring back to Table III, a similar lack of relationship can be noted between fur dye dust and paraphenylene diamine or oxidized aniline as represented in the results of the patch tests. No individual with positive fur dye dust skin reaction gave a positive patch test with paraphenylene diamine, and only one gave a positive patch test with oxidized aniline.

Of the ten patients in Group B-1 a causal relation with their occupational environment was finally proved in four. This was accomplished by clinical test with substances in their environment other than fur dye dust.

CONCLUSIONS

1. Positive reactions to intradermal tests with fur dye dust extracts were found in approximately the same percentage in allergic individuals within and without the fur industry.

2. Fur dye dust presents at least two constitutional elements, one relating it to, another differentiating it from, house dust. This differential element may produce a cutaneous reaction of the immediate variety and, therefore, its general chemical structure resembles that of other atopens also producing cutaneous reactions of the immediate variety.

3. A positive skin reaction to fur dye dust is of no greater significance in the etiology of symptoms than a like reaction to any other atopen.

4. To implicate fur dye dust decisively in a causal relationship with presenting symptoms, even in an individual with a prolonged history of contact, more evidence than a positive skin reaction is necessary.

5. The differential element in fur dye dust is probably not related to aniline dye or to paraphenylene diamine or to their alteration products.

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ALLERGIC MANIFESTATIONS IN ATOPIC INDIVIDUALS FOLLOWING INJECTION OF TETANUS TOXOID

Report of Two Cases

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THE study reported by Cooke and his co-workers[1] in May, 1940, on the sensitizing character of alum-precipitated tetanus toxoid, brought to the attention of the medical public the possibility of certain allergic side effects of active immunization with this material. Six cases were mentioned in this report, presenting a variety of symptoms localized, for the most part, in the skin, coming on after the second injection, mild in character, and short in duration. In these cases, skin sensitivity to toxoid persisted, in decreasing degree, from four to eight months. The authors emphasized the extremely low incidence of these post-injection manifestations, and also the fact that they were very mild. They suggested that toxoid scratch tests be used before the second injection, that positive reactions be followed with multiple divided doses of toxoid, that the subject be observed for one-half hour after each dose, and that adrenalin be at hand in event of a severe systemic manifestation.

Other reports have appeared in the literature describing allergic manifestations following toxoid injection. These have varied from anaphylactic shock to localized brawny swelling at the injection site. They have appeared after the first, second, or third injection, and have been momentary or prolonged, immediate or delayed. The greater proportion of these manifestations have been limited to the skin. These reports have emanated from the United States by Unger,[2] Sulzberger,[3] Rackeman,[4] Newell and McVea,[5] Bigler and Werner,[6] and Gold[7]; and from Great Britain by Donaldson,[8] Boyd,[9] Parish and Oakley,[10] Whittingham,[11] and Cunningham.[12]

The extreme rarity of these postinjection symptoms was pointed out by Boyd[9] and by Gold[7] in 1941 and, at the same time, the high incidence of positive reaction on intradermal testing with toxoid. Gold reviewed 1,700 cases actively immunized, and found only two with urticaria following the second or later injection. In Cooke's[1] series, there were two patients who developed urticaria after the second injection, in the absence of a positive skin test. Gold noted this disparity between the occurrence of positive skin reactions on testing, and the appearance of symptoms following injection. He concluded that the skin test with toxoid is of no practical value, whether positive or negative, as an indication for or against giving the toxoid.

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Donaldson,[8] Parish and Oakley,[10] Whittingham,[11] and Cunningham[12] reported nonfatal anaphylaxis following the second injection. Whittingham made a statistical survey of more than 61,000 immunizations. Only two had nonfatal, but severe, constitutional reactions, i.e., symptoms resembling anaphylactic shock; twelve had milder systemic reactions characterized by malaise, myalgias, slight pyrexia, with or without urticaria; and 651 had local reactions only such as brawny swelling and pain about the injection site for twelve to twenty-four hours, with or without urticaria and pruritis in the same area. Parish and Oakley's case of anaphylactic shock was one of 300 immunized, and gave a history of staphylococcic toxoid injection one and two years before.

The consensus of opinion indicts, as the sensitizing agent or agents, Witte and Berna peptone, and to a lesser degree Difco proteose, which are constituents of tetanus culture medium and therefore of toxoid. That the bacterial and toxin proteins also act in this manner has not been ruled out, but their role as sensitizing agents is minor. It has been recommended on these grounds that an effort be made to develop a culture medium eliminating these peptones, preferably an entirely synthetic one.

Sulzberger[3] reported a case of chronic urticaria, of six months' duration at the time of writing, the onset of which occurred three days after the first injection of alum-precipitated toxoid. Cooke also observed two cases with onset of symptoms after the first injection. Sulzberger presented two possible explanations for this reaction: (1) that the primary sensitivity to proteoses was developed by the injection, and the initiation and continuation of symptoms, by repeated exposures to proteoses of foods or inhalants, or of endogenous origin as represented by the catabolism of body proteins; (2) that a deposit of the injected alum-precipitated toxoid was formed, from which small amounts of allergen continue to escape over a long period of time.

It is not the scope of this paper to discuss these possibilities except to note that the latter is highly improbable, since alum-precipitated pollen extract has been used in the hope of just such a response so that the number of injections in the treatment of hay fever could be reduced radically. No noteworthy success has been attained. It is of moment that Sulzberger's case gave no atopic history nor was skin sensitivity to the ordinary allergens present. No reagins were found in the patient's blood.

In all of the cases reported in the literature, there was no attempt at classification into the general groups of atopic and nonatopic. It seems to the writer that this is an important point since, theoretically, the atopic group is more prone to sensitization.

The two cases herein described are given because of several unusual features in their symptomatology, and because of the problem presented in regard to future management.

CASE REPORTS

CASE 1.—E. W. L., a 27-year-old white male entered active duty on Oct. 10, 1941. On October 9 he received his first injection of fluid tetanus toxoid subcutaneously (1.0 c.c.). Within one week he developed small erythematous pruritic papules that appeared first on the forearms, then on the trunk, buttocks, calves, and ankles. This spread occurred gradually in one month. The papules broke on scratching, and oozed, relieving the itching. Crusting followed. During the night, under bedclothes, the itching increased markedly.

For several days after the next two toxoid injections, there was an increased pruritus. Large numbers of new papules appeared in the same areas mentioned above. The skin lesions, best described as a papular urticaria, appeared and disappeared until the present writing, January, 1943. As time progressed, the patient noticed a lack of oil-secreting function of the skin. Baths and showers, especially those warm or hot, caused generalized stinging and itching, and dryness and scaling of the skin. To circumvent these latter symptoms, the patient rubbed mineral oil into his skin after bathing.

Hot weather, exertion, or anything causing perspiration produced exacerbation of the lesions and pruritus that became unbearable and interfered with his work. Upper respiratory infections and excessive fatigue produced the same effects, the lesions always recurring in their original sites.

In January, 1942, he was inoculated with yellow fever and typhus vaccine. Several days later, he noticed a marked increase in severity of the dermatitis. He was hospitalized for two weeks at Station Hospital, where ultraviolet therapy was applied and aggravated the condition. He was then given adrenalin subcutaneously, and zinc oxide in oil and limewater locally. This relieved him somewhat, but the bandages applied, or any pressure on the skin caused the appearance of new lesions which wept copiously. He was discharged from the hospital with some alleviation of his condition.

On July 8, 1942, he was tested intradermally with 0.1 c.c. of toxoid. Five to ten large swellings with a wide zone of erythema appeared at the injection site. In several days, this arm and the contralateral arm presented showers of papular urticarial lesions, erythematous and extremely pruritic.

On August 19, he arrived in England, where, because of the cool weather (patient's own assigned reason), his condition improved. He was eventually hospitalized there because he sought to have the fact of his toxoid sensitivity placed on his identification tags. He was then sent to Tilton General Hospital for observation and disposition, arriving on Nov. 14, 1942.

His past history is of interest. From childhood he suffered with an irritable skin which welted markedly when scratched or subjected to minor traumata or steady pressure. He also had mild rhinitic symptoms

unrelated to the season of the year or to upper respiratory infection. He had many bouts of poison ivy dermatitis. He gave no history of clinical allergic manifestations previous to his entry into the army. Several months before his toxoid injections, he received a series of injections for typhoid immunization.

A significant family history was obtained. His mother, one sister, and one brother have severe hay fever. One brother has asthma. His mother has always had a sensitive skin.

Physical examination made overseas on Nov. 14, 1940, was essentially negative except for skin lesions on the calves, buttocks, and intergluteal folds, with smaller ones on the arms. These were described as eroded papular lesions, pruritic, and with a tendency to weep.

Physical examination at Tilton General Hospital one month later was also essentially negative except for the skin, on which was found a circinate, chronic, dry, papular eruption of lichenified dermatitis on an erythematous base. The individual lesion was about the size of a quarter, markedly pruritic. Distribution was on both feet and legs, and on the anterior and posterior surfaces of the thighs.

Roentgen rays of the chest and sinuses were normal. No abnormalities of the blood chemistry, serology, or urine were found. The blood picture was normal with 3 per cent eosinophiles.

The allergic investigation was extremely interesting. Intradermal tests with the usual complement of allergens (over 110) revealed many positive reactions of moderate degree, including inhalants and ingestants. Tetanus toxoid diluted 1:100 gave a 3 plus reaction. Moderate pressure and slight friction of the skin produced large welts. Light pressure had no effect. The patient's serum was prepared for passive transfer. The transfer subject was tested to the full complement of allergens and found entirely skin test negative. Twenty sites on the skin of his arm were sensitized with the patient's serum and tested with all of the allergens which had been productive of positive reactions on direct intradermal testing of the patient. Most of these reactions were reproduced on the transfer sites in lesser degree. The toxoid 1:100 did not transfer. Toxoid 1:10 transferred 1 plus. Toxoid undiluted transferred 3 plus.

Before the allergic investigation was begun, the patient was placed on crude coal tar ointment for two weeks, during which time his dermatitis cleared up except for a few areas of pigmentation which were interpreted as the result of long-standing and repeated minor infection.

Since the patient was an officer in the Corps of Engineers and therefore likely to be exposed to dirty wounds, the necessity of reinjecting with a stimulating dose of tetanus toxoid was discussed. Gold[13] pointed out the efficacity of topagen (toxoid by intranasal route) in rebuilding antitoxin titer. The standard equipment of the army, however, is subcutaneous toxoid, and in the field where speed is a prime factor, no one individual can be singled out for unusual or radically different therapy.

The problem remained to nullify the risk of reinjection and return this officer to his previous efficiency by eliminating or reducing the recurring dermatitis.

On Dec. 1, 1942, the patient was given 0.2 c.c. fluid tetanus toxoid diluted 1:100 with Coca's fluid. Within five minutes there was a slight swelling at the site of injection and, shortly thereafter, the appearance in this area of many small papules. This was followed by pruritus of the back and legs, transient in nature. The next day twice this dose was given, with the same slight after effects. The following day 0.8 c.c. of the same dilution was given. The injection site swelled to the size of one-half dollar, pruritus appeared generalized within two hours, and the sites of the lesions previously existing revealed exacerbation. Attempt at hyposensitization was discontinued, and the patient was given a thirty-day sick leave.

When he returned, the lesions had almost entirely disappeared except for their presence in a new area, the glans penis. The patient stated that, after intercourse with his wife, he noticed that the glans began to swell and in a short while the lesions began to appear. On inspection, only remnants of small papules were discernible on the glans and inner surfaces of the prepuce. He stated also that on the train ride home he rested his elbow on the window sill until pruritus and heat called his attention to it, and he found it red and swollen. It remained so for a few hours only.

On Jan. 8, 1943, another attempt at hyposensitization was made. He was given 0.1 c.c. of a 1:10,000 dilution of tetanus toxoid. This dose was increased daily until February 1, when he received 0.8 c.c. of undiluted tetanus toxoid without any after effects. Thus, in a three-week period he had received almost 2 c.c. of toxoid, which constituted his stimulating dose. He had reached an optimum of antitoxin titer. The remaining problem was to maintain the patient in such a manner that whenever need be, he could receive a single injection of toxoid, 1 c.c., without ill effect. It was recommended that he be discharged from the hospital to receive, at his station, weekly injections of tetanus culture medium. This interval could gradually be increased to one month, until the next stimulating dose of toxoid was due (six months to one year).

Since the patient was atopic, it was felt, in explanation of his postinjection manifestations, that his nonclinical sensitivity to various inhalant and ingestant proteoses had become activated by the sudden large injection of toxoid. This activated clinical sensitivity continued its manifestations in greater or lesser degree by virtue of continued contact with these proteoses. It was recommended, therefore, from the viewpoint of his dermatitis, that he be placed on a diet eliminating the various foods to which he showed positive reactions and which tested positively on passive transfer sites. The end results of this therapy

will be reported at a later date. (The writer wishes to point out that the treatment in this case, i.e., hyposensitization with toxoid, and the proposed further therapy with tetanus culture medium, is neither a routine procedure nor an ordinarily acceptable one in the army. It is obvious that the rarity of cases requiring such therapy, and the lack of data relative to results of such therapy, would make the procedure an individual one and its acceptance by the army questionable.)

CASE 2.—M. J., 31 years of age, a white female nurse, entered active duty on Oct. 1, 1942 and received her first immunization injection of tetanus toxoid (fluid) on the same date. On October 23 she was given her second injection. Twenty-four hours later she noticed a mild pruritus of the neck, arms, and legs. Scratching produced raised red lines. This was of such minor degree that she paid little attention to it. Thirty-eight days later, she was given her third injection. Within forty-eight hours she developed a marked generalized pruritus that brought her to the dispensary for medical aid. She stated at this time that the slightest pressure or friction applied to her skin, such as the rubbing of her collar against her neck or the scratching of the pruritic areas, produced marked welting with an increased pruritus and a sensation of heat. This condition continued unabated and interfered with her normal efficiency at work. Then, on the night of December 29, she bit her lower lip while eating. The next morning she awakened with a marked swelling of the lower lip. Questioning revealed that the area of swelling coincided with that bitten. The swelling was so large that she was confined to bed and given adrenalin subcutaneously and repeated doses of ephedrine sulfate orally. With this therapy the swelling subsided in twenty-four hours. The next day the right thenar eminence swelled to such a degree that she could not use her right hand. As physiotherapist, part of her daily task was to wring out cloths. She stated that she may have used undue pressure on this occasion. The swelling disappeared in twelve hours. Two other episodes of marked swelling occurred, one of the tongue and the other of the lateral aspect of the left foot. Each remained twelve to twenty-four hours. From the onset to date, the generalized pruritus and welting on friction have continued in decreasing severity, and for the past several weeks the patient has been able to work without much discomfort.

The past history reveals the usual childhood diseases. In 1938 she had lichen planus for two months. There had been no previous toxoid injections, but three typhoid series had been given, in 1936, 1941, and 1942, respectively. Careful questioning revealed no injections whatsoever in childhood. The significant part of her past history related to mild rhinorrhea and sneezing whenever she went to the country in summer or fall, or when, during the course of housework, she swept or dusted. She averred a lifelong distate for shellfish. After this questioning, however, she ate nine fried oysters without any ill effects.

The family history was not definite. Her mother experiences slight difficulty in breathing when in the country during the summer or fall. One nephew has bronchitis.

Allergic investigation revealed marked hypersensitivity of the skin to the mildest friction or pressure. Needle puncture produced moderate whealing and marked erythema. Direct testing was, therefore, impossible. Her blood was prepared for passive transfer. Twenty sites on the arm of a subject previously proved skin-negative to the full complement of allergens by intradermal test were sensitized with her serum. These sites were then tested, and many positive reactions to inhalants and ingestants were obtained. All of the shellfish showed 3 or 4 plus reactions. Several tree pollens transferred 2 plus. Timothy, plantain, and ragweed were negative up to 1,000 units. Toxoid 1:10 was 2 plus; toxoid undiluted was 3 plus.

Herewith is presented another atopic individual with subclinical or, at most, extremely mild clinical hypersensitiveness.

COMMENT

Although these two cases present some striking similarities in symptoms and background, the relationship to toxoid injection is different. In E. W. L., skin irritability was present before toxoid injection; in M. J., it appeared after toxoid injection. In E. W. L., symptoms appeared after first injection; in M. J., after second injection and more markedly after third. In the case of M. J., the positive passive transfer, the suggestive past, and the family history definitely label her an atopic individual. It is suggested that here again symptoms were precipitated by toxoid, and perhaps continued by previously existing subclinical sensitivity to allergenic proteoses in her normal environment. Whether or not sensitivity to toxoid was perpetrated by the injection or pre-existed in sub-clinical form, by virtue of the similarity between lytic products of inhalant and ingestant proteins and tetanus toxin culture medium, is a moot question. In this case, unfortunately, circumstances have prevented the institution of therapy.

These cases were similar in other aspects also, namely: unnoticed minor clinical manifestations of sensitivity; presence of reagins in the bloodstream; persistence of symptoms, and their aggravation by heat, exertion, baths, and friction. A major presenting symptom was hypersensitivity of skin to irritation. The cases differed in duration of symptoms, and in the fact that the symptoms of one came on after the first injection, and those of the other after the second injection.

It is noteworthy that in this hospital, a military installation where tetanus immunization is given daily and where all of the patients admitted have been immunized, only two cases in the course of one year have presented themselves in either the dispensary or the ward with manifestations attributable to these injections. The rarity of such manifestations is obvious. That many cases of extremely minor symptoms go unnoticed, primarily because they are not impelled by discom-

fort to seek medical aid, is an assumption that can neither be denied nor affirmed. The analysis of Whittingham,[11] referred to above, would favor denial.

Both of these cases proved to be atopic. It is tempting to postulate that such reactions occur in atopics, with or without clinical sensitivity, in the greater majority of cases. It certainly would seem, using Sulzberger's[3] theoretical explanation, that the toxoid in these cases precipitates a pre-existing sensitivity rather than itself sensitizing; or, if it sensitizes primarily, that it is more apt to do so in the atopic individual, by virtue of his very immunochemical or physiologic constitution.[14] It is to be noted that *fluid* tetanus toxoid and not alum-precipitated toxoid was used for immunization here. Long[15] pointed out the reason for the use of this variety of toxoid in the United States Army. The culture medium employed is protein in nature, and therefore not entirely free of proteoses; however, Berna and Witte peptone are absent. This fact, in addition to the inherently smaller sensitizing potential of fluid toxoid compared to alum-precipitated toxoid, underlines the probability of allergic manifestations on a basis of pre-existing proteose sensitivity.

SUMMARY

1. Two cases of sensitivity to fluid tetanus toxoid in atopic individuals are reported.

2. Manifestations in one patient have persisted more than two years.

3. In one case, hyposensitization with fluid toxoid produced marked symptomatic improvement.

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ANAPHYLAXIS AFTER INJECTION OF TETANUS TOXOID

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SINCE the first attempt at active immunization to tetanus in man by Bazy[1] in 1926, severe reactions have been reported, but their prevalence has been minimized. Whittingham[2] surveyed the reactions among 61,042 individuals in the Royal Air Force immunized with plain tetanus toxoid, and found two cases of acute anaphylactic shock (0.003 per cent), 12 cases of constitutional reactions (0.02 per cent), and 651 cases of local reactions (1.06 per cent). Hall[3] reported that among 2,300 students at the United States Naval Academy, immunized with alum precipitated toxoid, there were 11 reactions (0.47 per cent) following the initial injection. These reactions comprised 8 cases of sore arms, 2 cases of malaise and fever, and one generalized urticaria. A second dose administered eight weeks later to 1,800 students resulted in 50 reactions comprising 38 cases of sore arms, 7 cases of malaise and fever, 4 cases of generalized urticaria, and one frank anaphylactic shock. As a result of the large number of reactions following the second dose, the brand of toxoid was discontinued and another substituted on the remaining 500 students without any reactions. The following year the incoming class of 793 students was immunized with alum precipitated toxoid, with one case of malaise and fever developing after the first dose, and no reactions after the second. Gold[4] reported one systemic reaction from using an alum precipitated toxoid among 1,000 immunizations given over a five-year period. Jones and Moss[5] had two cases of severe local reactions among 58 immunizations with alum precipitated toxoid. Cases of severe generalized reactions have been reported by Whittingham,[2] Parish and Oakley,[6] Cunningham,[7] and Cooke et al.,[8] all of whom were of the opinion that the responsible agent was the peptone contained in the media which were used in the preparation of the toxoid.

The following case of an anaphylactoid type of reaction, which occurred after the administration of plain tetanus toxoid, is considered worthy of reporting.

CASE REPORT

M. S., a white man aged 29 years, was admitted to the Medical Service, Letterman General Hospital, Feb. 2, 1942, complaining of epigastric pains. The onset of the pains was preceded by a third injection of tetanus toxoid (brand A, control number 6019) administered Jan. 27, 1942 at a batallion aid station. Two previous doses given at three-week

From the Medical Service, Letterman General Hospital.

intervals had produced no symptoms. Twenty minutes following the third injection, his eyes and lips became swollen and he experienced a feeling of faintness and collapsed. He remained unconscious for approximately twenty minutes. A tourniquet was applied above the site of injection by the attending medical officer, and 0.5 c.c. of epinephrine hydrochloride was administered subcutaneously. A second dose was required later. There was no record of the temperature, pulse rate, or blood pressure. After regaining consciousness he complained of sharp intermittent epigastric pains, for which it was necessary to confine him to a clearing station. He was later transferred to Letterman General Hospital when the pains did not subside.

Family History.—The patient's father died as a result of drowning. The mother was living and well. A maternal grandmother had asthma. There were two siblings living and well. He had two children living and well, and one child with congenital spastic paraplegia.

Personal History.—The patient was a sergeant in a coast artillery unit. Prior to induction he had been employed as a shipping clerk. Past illnesses comprised measles and mumps in childhood. He had received typhoid vaccine in 1941 without any untoward symptoms. For the past few years he had complained of vague, inconstant, generalized abdominal pains which, however, had never incapacitated him. He denied any specific food intolerance. There was no past history of asthma or hay fever.

Physical Examination.—The temperature, pulse rate, and respirations were normal. The blood pressure was 114/70 mm. Hg. There was an area of redness and swelling at the site of the toxoid injection on the left arm. The physical examination was otherwise essentially normal.

Laboratory Findings.—White blood cells 9,900, red blood cells 5 million, hemoglobin 92 per cent differential count normal. The urine was normal. Serology was negative. Heterophile antibody titer for sheep cells was negative.

Skin Tests.—He was skin tested by the scratch and intradermal methods with the routine diagnostic allergens including trees, grasses, weeds, epidermals, inhalants, molds, house dust, and respiratory vaccine. There were marked intradermal reactions (3+) to milk, beef, lamb, and salmon (all 0.1 mg. N.). There were moderate intradermal reactions (2+) to mixed feathers and house dust. Four commercial brands of plain tetanus toxoid (A,B,C,D) in bulk undiluted were applied, and marked intradermal reactions (3+) resulted with all. Through the kindness of the Squibb and Lederle Laboratories, the individual ingredients of their respective toxoids were supplied for intradermal skin testing. Marked reactions (3+) were obtained with the peptone component, the complete toxoid media, and the beef heart, supplied by the manufacturers of brand B. Marked reactions (3+) also resulted with Witte's peptone and veal infusion supplied by the manufacturers of brand D. The

individual ingredients of brands A and C could not be supplied, but correspondence with the firm supplying brand A which the patient received, revealed it to contain veal infusion and peptic meat digest.

Skin tests with the toxoids and their ingredients are shown in Table I.

TABLE I

SKIN TESTS DEMONSTRATING SENSITIZATION TO TOXOID AND INGREDIENTS
Patient M. S.

TESTED WITH	RESULT	CONTROL
Brand A (undiluted)	+++	0
Brand B (undiluted)	+++	0
Peptone component	+++	0
Beef heart extract	+++	0
Complete toxoid media	+++	0
Brand C (undiluted)	+++	0
Brand D (undiluted)	+++	0
Witte peptone	+++	0
Veal infusion	+++	0

Passive Transfer Studies to Human Skin.—The patient was bled, and 0.05 c.c. of serum was injected intracutaneously into a normal subject at sites along the arm. These prepared sites were tested forty-eight hours later, using 0.02 c.c. amounts of the routine diagnostic allergens to which positive skin tests had been obtained in the patient. Similar amounts of the four commercial brands of toxoids (A,B,C,D) in bulk undiluted, and the individual components of brands B and D were likewise injected into sites on the arms of the subject. Immediate moderate reactions (2+) were obtained with milk, beef, lamb, beef heart (brand B), veal infusion (brand D), and to brands A,C, and D. There were slight reactions (1+) with the peptone component (brand B), complete toxoid media (brand B), Witte's peptone (brand D), and to brand B in bulk. Thus, the presence of skin-sensitizing antibodies for milk, beef, lamb, and the substances in the tetanus toxoid preparations was demonstrated in the serum of the patient.

Passive transfer studies with the toxoid and their ingredients are shown in Table II.

TABLE II

PASSIVE TRANSFER TESTS TO HUMAN SKIN: QUALITATIVE

M.S. SERUM SITES	TESTED WITH	RESULT	CONTROL
1	Brand A (undiluted)	++	0
2	Brand B (undiluted)	+	0
3	Peptone component	+	0
4	Beef heart extract	++	0
5	Complete toxoid media	+	0
6	Brand C (undiluted)	++	0
7	Brand D (undiluted)	++	0
8	Witte peptone	+	0
9	Veal infusion	++	0

Course in Hospital.—The epigastric pains gradually subsided a few days after admission, but the patient was observed on the wards for two weeks. He was warned of the danger of receiving a stimulating dose

before first making his sensitivity known to the medical officer responsible for the injection. A gastrointestinal series revealed no organic lesions to account for his pains. He continued to remain asymptomatic and was returned to duty.

DISCUSSION

The development of edema of the eyes and lips, followed by collapse, in a 29-year-old man who had received a third injection of plain tetanus toxoid is obviously an anaphylactoid type of reaction. This is substantiated by skin tests and passive transfer studies to human skin. The ingredient contained in the toxoid which is responsible for the reaction is questionable since positive skin tests and passive transfer tests were obtained with all the available ingredients. Positive passive transfer reactions with the antigenically closely related beef, beef heart, and veal infusion, point to the latter, which was present in brand A and administered to the patient as the offending factor. This cannot be definitely ascertained, however, since the peptic meat digest, also present in brand A, was not available for skin testing. It is interesting that there was no history of asthma or hay fever in the patient, and his skin tests with the diagnostic allergens, which included trees, grasses, weeds, epidermals, and inhalants, were all negative. This demonstrates that severe reactions do occur in the absence of a history of obvious allergy known to the patient. The cause of the epigastric pains following the administration of the toxoid is not clear, but the absence of any demonstrable gastrointestinal pathology suggests that they were part of the toxoid reaction. Cooke et al.[8] pointed out that all persons receiving tetanus toxoid should first be skin tested, and this seems quite appropriate in the case presented. Gold[9] discourages skin tests, and cites two patients of Cooke's who had generalized urticaria in the absence of positive skin tests, and conversely, four patients in his own series who gave significant positive skin tests with toxoid and received injections without any untoward symptoms. The apparent indifference of Gold to positive skin tests is certainly not shared by all engaged in allergy. The writer[10] observed the sudden death of a young person to whom no previous sensitivity tests had been applied, twenty minutes after the injection of a second dose of plain tetanus toxoid combined with a third dose of typhoid vaccine. Artificial respiration and administration of epinephrine were of no avail, and autopsy revealed the presence of pulmonary edema. To minimize the significance of a positive skin test, and then unhesitatingly, administer the full dose parenterally, is definitely contrary to the orthodox practice.

SUMMARY

1. A case of severe reaction to tetanus toxoid has been presented.

2. The incidence of severe reactions taken from the literature has been reviewed.

3. Allergy studies carried out in the case presented point to the veal infusion contained in the toxoid as the responsible factor.

4. A severe reaction which resulted in death following the administration of tetanus toxoid has been cited.

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AN APPRAISAL OF THE PRESENT STATUS OF PROPHYLAXIS AGAINST POISON IVY

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THE prophylactic treatment of poison ivy dermatitis has been extensively investigated for many years. Injections and oral administration of the oleoresin for prophylaxis against poison ivy dermatitis were introduced in 1918 by Strickler,[1] and in 1919 by Schamberg.[2] At the present time, however, the majority of dermatologists regard prophylaxis as of questionable value. Some investigators have reported successful desensitization of patients to poison ivy. Their results were based mainly on the appraisal of the clinical response; the fact that patch tests showed little if any reduction in sensitivity was not considered in the evaluation of the so-called desensitization. They compared patch testing to the intradermal reaction obtained in atopic diseases such as hay fever, in which the clinical improvement frequently is not accompanied by a decrease in the skin reaction. They reasoned that clinical response was independent of the results of patch tests. In poison ivy dermatitis both the patch test response and the eruption are due to the topical application of the sensitizer; but in the clinical exposure the quantity and strength of the antigen remaining in contact with the skin cannot be controlled.

Shelmire demonstrated[3a] that patients who are sensitive to the oleoresin or the antigenic agent of poison ivy are also sensitive to poison oak, and the poisonous type of sumac. The undiluted milk sap of poison ivy is a primary irritant or escharotic and will cause an eschar when applied undiluted to the unsensitized skin. It is difficult to compare the findings of one investigator with those of another because there are no standards for the potency of poison ivy extracts. Shelmire[3b, c] cited the cases of some patients who were sensitive to a 1:1,000,000 dilution of his extract. The commonly used or average extracts at this dilution would probably not cause a reaction in a sensitized person. Keeney and his co-workers[4] concluded that patch tests performed with a 1:25 peanut oil dilution of their ether extract of fresh leaves and stems of the poison ivy plant accurately revealed hypersensitiveness. Stratton[5] attempted to determine the dermatitant units for these extracts. He "selected as representing 10,000 dermatitant units that quantity of poison oak or poison ivy extract contained in 0.1 c.c. of designated solvents, which, when applied without cover to the epilated skin of animals which do not become sensitized, such as the rabbit, rat, or mouse, in the form of a stripe, is just sufficient to elicit an erythematous reaction within forty-eight hours." The difficulty with this standard is that it is biologic

and has not been confirmed. The potency of an extract will depend on the source of the raw materials (extracts from roots are more potent than extracts from leaves). It varies with the seasons of the year, the oil solvent used, the manner of preparation, the age, the method of storage and the areas tested. Lehmann[6] listed thirteen authors who reported favorable results, and five who reported unfavorable responses to the prophylactic use of injection of poison ivy antigen. Successes are more apt to be reported than failures. In 1933, Gowen[7] stated, "One injection in the spring will protect susceptible individuals for approximately one year as shown by four of the reported cases." Spain and Cooke[8] who performed excellent experimental work with a poison ivy antigen, considered the oral administration to be unsatisfactory, but wrote, "Although the patient received daily oral treatments for the first five months and regular weekly injections for the next eight months, no change whatsoever in the reaction of the skin was apparent; and, since the result clinically was successful, it must be concluded that the degree of immunity developed by treatment cannot be determined by a change in the cutaneous reaction. This condition is, of course, analogous to that found in hay fever." They concluded that "the development of a clinical degree of immunity, as a result of treatment, is indicated by the history of improvement, and not by any demonstrable change upon tests in the reaction of the skin toward the active principle." Blank and Coca[9] observed the effects of four weekly injections of several strengths of extracts and stated that "injections of an extract of poison ivy can establish a complete immunity to the usually direct contact with the plant in at least a considerable proportion of susceptible persons." This conclusion was based on clinical data only. Gay, in the discussion of Keeney's[10] recent presentation stated, "Oral treatment is questionably successful; in fact, I think one can consider it a failure, but the prophylactic treatment by the injection method is extremely satisfactory. Dr. Keeney did not emphasize the fact that after treatment with the ether extract a number of our patients showed diminished skin reactivity." Caulfeild[11] administered eight to twenty-six injections to patients and reported a satisfactory reduction in quantitative patch tests and an increase in clinical immunity.

A few adverse opinions are cited. Bachman[12] found that three injections in fourteen children were of no value as treatment or as prophylaxis against poison ivy. Krause and Weidman[13] considered four injections of no value. Simon and Lotspeich's[14] report was unfavorable Zisserman and Birch[15] studied a group of 1,731 boys; 304 were given injections of antigen; dermatitis venenata developed in 51.6 per cent in the treated group, while the incidence in the untreated group was 33.6 per cent. They concluded, "It would seem that, in general, the incidence of dermatitis increased as the amount of therapy increased." The wide divergence of these conclusions are interpreted as showing that the oral

administration and the injection of the antigen as usually given are of no value in the prevention of poison ivy.

Keeney[10] stated that a positive patch test caused a refractory period for six to eight weeks in the tested area. Krause and Weidman,[13] Shelmire,[16] and the author could not demonstrate such a refractory stage in a previously positive patch-tested area. The persistance of the pruritus ani following the ingestion of poison ivy tablets also disproves that a local reaction causes a local immunity.

Within the last few years, Shelmire[3] has recommended a modification of the oral prophylactic treatment of poison ivy originally introduced by Strickler[1] and Schamberg[2] in 1918 and 1919. He recommended long courses of treatment with potent extracts in corn oil in daily ascending doses, and demonstrated that the antigen is readily absorbed from the intestinal tract. Shelmire stated that the amount of antigen that could be taken by mouth in two and one-half months was equal to the amount that could be injected over a period of sixteen to three hundred years. After two to nine months of oral therapy, Shelmire obtained negative patch tests with a 1:10 potent extract in eight susceptible patients. Gold and Masucci[17] introduced the use of coated tablets of ether extracts of poison ivy antigens, which had the advantage of ease of administration and of more accurate dosage. They increased rapidly the ingestion of the extract, so that within forty-five days a daily dose of 150 mg. was reached. Gold and Masucci stated that after forty-five days of treatment, negative patch tests were obtained in three of twenty patients, and several others also showed signs indicating decreased sensitivity. Schwartz,[18] of the Public Health Institute, found that the seven individuals who completed the two- to three-month course of poison ivy immunization showed improvement in their degree of sensitivity, as demonstrated by postimmunization quantitative patch tests. Most of Gold and Masucci's and Schwartz's patients developed annoying pruritus ani, and many had generalized eruptions.

AUTHOR'S EXPERIENCE

Five patients have been treated by the oral administration of the ether extract of poison ivy tablets* as used by Gold and Masucci. Pretreatment quantitative patch tests were made before the prophylactic therapy to poison ivy was started. Four of the patients were adults.

CASE REPORTS

CASE 1.—A boy, aged 5 years, had had several severe attacks of poison ivy during the past three summers. Patch tests demonstrated that he was sensitive to the rhus tox extract. He was started on 0.5 mg. tablets and the dose was slowly increased so that within sixty days he was ingesting 10 mg. a day. The child developed no complications or made any complaints about the oral therapy.

*Sharp and Dohme, Inc.

CASE 2.—A white girl, aged 20 years, had recently had several severe attacks of poison ivy dermatitis. Patch test with 1:100 rhus toxin caused a positive reaction. On June 28, 1942, she ingested a 0.5 mg. tablet of poison ivy extract, on June 29, 1 mg., and on June 30, 1.5 mg. On the fourth day the dose was increased to 2 mg. On that day (July 1), she complained of generalized itching which was severe enough to keep her awake at night. The tablets were discontinued. After the itching had subsided, she took 2 mg. of the extract on July 7, 8, and 9. She complained again of severe generalized itching, and of numerous noninflammatory, small, sagolike, deep vesicles which appeared on the hands and fingers, especially in the palmar surfaces. Subsequently there was exfoliation of the skin of the hands. The patient refused further therapy.

CASE 3.—A 40-year-old white man had had many severe attacks of poison ivy dermatitis as a boy, but only mild attacks in the past few years. It had been shown by previous patch tests over a period of years that he was sensitive to poison ivy. In June, 1942, a 1:100 dilution of an antigen in oil, when applied as a covered patch test for twenty-four hours, caused an immediate positive 3+ reaction; 1:1,000 gave a positive 2+ reaction (erythema with moderate infiltration), and 1:10,000 gave a 1+ delayed reaction of erythema. On June 13, 1942, the patient was started on a course of ether extract of poison ivy tablets. The doses were as follows: first week; first day, 0.5 mg.; second day, 1 mg.; third day, 1.5 mg.; and 2 mg. thereafter for four days. Therapy was stopped for a few days because of pruritus ani, generalized itching, and plaques of a slightly vesicular, erythematous, pruritic dermatitis in the inguinal regions, and in the left, posterior, axillary fold. At this time, patch tests to 1:10,000 and 1:1,000 dilutions of the antigen caused no reactions, but 1:100 gave a positive test. On June 23 (ten days after the first dose), therapy was resumed with the ingestion of 2 mg. per day. Two days later a severe pruritus ani was present, and five days later therapy was again discontinued for two days because of generalized and anal itching. During the third week this patient ingested 5 mg. daily, and during the fourth and fifth weeks, 10 mg. daily; sixth week, 15 mg., and for the next three weeks, 20 mg. per day. During the following eighteen days he took 25 mg. per day, and six months later he was taking 500 mg. per day. The total amount ingested up to Nov. 30, 1942, was 13,000 mg. Several times early in the course of treatment the antigen was discontinued for a day or two because of a localized dermatitis in the inguinal regions, generalized itching, or pruritus ani severe enough to cause insomnia. After five months of oral tablet therapy a patch test with a 1:100 dilution of the original antigen gave a negative reaction, but a 1:100 dilution of a more potent antigen gave a delayed erythema without infiltration or vesiculation, and a 1:20 dilution caused an immediate positive 3+ reaction. During the first part of the sixth

TABLE I

SUMMARY OF CASE 3

1942	MG.	SYMPTOMS	PATCH TESTS
6/13	0.5	None	1:10,000 Antigen A 1+
6/14	1	None	1:1,000 Antigen A 2+
6/15	1.5	None	1:100 Antigen A 3+
6/16	2	None	
6/17	2	Pruritus ani 1+	
6/18	2	Pruritus ani 2+	1:10,000 Antigen A -
6/19	2	Generalized itching	1:1,000 Antigen A -
	Rest	and localized dermatitis	1:100 Antigen A 3+
6/23	2	None	
6/24	2	None	
6/25 to 7/ 2	4	None	
	4	Pruritus ani 2+	
7/ 3 to 7/10	5	Mild pruritus ani	
7/11 to 7/25	10	Increased itching	
7/26 to 8/ 1	15	Itching subsiding	
		Slight pruritus ani	
8/ 2 to 8/30	20	Local and generalized itching	
		Itching subsiding	1:100 Antigen A 1+
8/31 to 9/10	25	Moderate symptoms	1:20 Antigen B 3+
9/11 to 9/20	30	Symptoms less annoying	1:100 Antigen B -
9/21 to 9/24	40	No complaints	1:50 Antigen B ±
9/25 to 10/1	50	No complaints	1:20 Antigen B in acetone 3+
10/ 1	60	None	
10/ 2	70	Pruritus ani ±	
10/ 3	80	Pruritus ani ±	
10 /4	90	None	
10/ 5	100	None	
10/ 6	110	None	
10/ 7	125	None	
10/ 8 to 10/12	150	Pruritus ani ±	
		Generalized itching ±	1:100 Antigen B ±
10/12 to 10/15	200	None	
		Total 3,250 mg.	
10/15 to 11/17	150	None	
		Total 8,000 mg.	1:50 Antigen B ±
11/19	200		1:20 Antigen B 2+
11/20	250		
11/21	300		1:100 Antigen C in acetone 2+
			1:100 Antigen A in alcohol -
11/22	350		
11/23	400		
11/24	500		
11/25	600		
11/26 to 12/1	500	No symptoms	
		Total 13,000 mg.	In acetone 1:100 antigen C -
			1:20 Antigen B ± (delayed)
			1:20 Antigen in acetone 1+

The antigens were dissolved in peanut oil unless otherwise stated.

The height of the reaction was taken as the reading, although it may have been delayed for several days.

From April 10, to April 19, 1943, the patient described in Case 3 ingested 1,600 mg. of the antigen. The highest daily dose was 500 mg. The only reaction was a mild pruritus ani. Patch tests to antigen "B" in oil gave a negative test to 1:500 dilution and 1 plus to 1:100 dilution. Following clinical exposure on April 17, 1943, he developed a moderately severe dermatitis venenata on the left hand and wrist.

month of therapy, the dose was increased rapidly to 500 mg. per day. On November 30, the reaction to 1:100 and 1:50 in oil of the more potent extract gave a completely negative reaction, and a 1:20 dilution of this extract in acetone gave a 2+ slightly delayed reaction. Six hundred mg. of poison ivy extract a day did not cause any local or generalized symptoms.

COMMENT

Many questions still remain unanswered. Does an increase in clinical immunity and in the general tolerance parallel a decrease in the reaction to patch tests? How much antigen must be ingested before sensitivity is depressed sufficiently to give clinical immunity? Does a negative patch test to a 1:25 dilution of a potent antigen accurately demonstrate this clinical immunity? What percentage of the extract taken by mouth is absorbed? It is the author's opinion that, with proper precautions, sufficient extract can be ingested to cause a decrease in patch test sensitivity to a level that is indicative of clinical immunity. The course of treatment may have to extend over a period of many months, and only patients with the history of severe disabling attacks of poison ivy would be willing to carry out the long prophylactic treatment necessary to give immunity.

SUMMARY

The study of the literature dealing with the prophylactic treatment of poison ivy antigens suggests that this treatment is of doubtful or no value. The most promising results are those of Shelmire who reported favorable response to oral therapy with a potent antigen in corn oil administered over long periods of time.

The use of the poison ivy extract tablets by mouth may be a more practical method of giving this drug. It is suggested that the dose should be increased gradually, and short rest periods be given when annoying symptoms appear. The extract may be resumed at the same dose that was being taken when the rest period was started. The fact that the dose can be gradually increased without recurrence of the anal or general itching suggests that there is an increase in tolerance. A decrease in the reaction to patch tests has been observed. The ingestion of the extract is of no value in the treatment of an attack of poison ivy dermatitis.

CONCLUSION

1. The use of extracts of poison ivy antigen in tablet form is a very convenient method of giving accurate doses by mouth.

2. Some of the antigen is absorbed because poison ivy sensitive patients frequently develop generalized symptoms early in the course of desensitization when 1 mg. or less is ingested.

3. Pruritus ani is a persistent and annoying complication.

4. One patient gradually developed marked immunity as demonstrated by negative patch tests to a 1:50 dilution of a potent extract. The total of 13,000 mg. of poison ivy extract tablets was ingested before negative patch tests were obtained to the more concentrated potent antigens.

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ALLERGY IN THE INSANE

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THERE seems to be an impression among psychiatrists and allergists that the incidence of the various allergic states in the insane is very small. Vaughan[1] quotes the head of one mental institution as stating that among 3,000 persons, only eight had clear cut allergic manifestations, and another as stating that of 2,500 persons, only five had asthma. On the other hand, Vaughan also quotes Walzer to the effect that hay fever is not uncommon among psychotics. Peters,[2] in a review of 4,500 cases, states that only six cases of allergy could be found, and of the six cases, only four gave positive reactions to skin tests. MacInnis[3] describes three of five psychotic patients whose allergy improved or disappeared during mental imbalance, with return of symptoms upon the approach of mental balance. She also states that a survey of more than 7,000 psychotic patients revealed five, or 0.07 per cent, with allergic symptoms. Vaughan[1] quotes Gillespie, who cites cases of manic-depressive psychosis without asthma when mental symptoms were present, but having it when mental symptoms subsided, and cases of dementia praecox in which asthma ceased at the onset of severe mental symptoms.

According to Tuft,[4] the incidence of hay fever is between 1 and 2 per cent of the population of the United States. He gives the same figures for asthma. Feinberg[5] also gives the incidence of hay fever as approximately 1 to 2 per cent of the American population. Criep[6] states, "It is estimated that about 3 per cent of the population have hay fever." Spain and Cooke[7] assert that 3.5 per cent of the population of this country are subject to hay fever or asthma at some time in their lives.

Our own interest in this subject developed during a search by one of us for allergic states in the insane, for the purpose of making certain studies. To our surprise, we were informed that, in a population of 3,000 persons in one institution, there were no cases of hay fever or asthma. Inquiry at a second mental institution with a population of 4,000 persons disclosed only one case of hay fever and no asthma.

This investigation is not concerned with the psychosomatic aspects of allergy in the sane, nor the effects of the nervous system, except as it may occur in the insane.

The reports dealing with the incidence of allergy in the insane do not describe methods of study to determine the figures. In our inquiries at the two institutions, the figures quoted to us were simply impressions

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not substantiated by study. This, apparently, is the case also in other reports of this type. The reports dealing with improvement of the allergy as insanity increased, and aggravation of the allergy as sanity returned, do not detail the type of allergic study done, if done at all, in most instances. For these reasons, therefore, it was decided to test a group of psychoties, taken at random without particular selection, with a series of antigens of high degree of known accuracy from a diagnostic standpoint. This was particularly necessary, for in most instances the patient's history was not only undependable, but unobtainable as well, due to the abnormal mental status.

For this purpose, scratch tests with pollens of elm, oak, June grass, timothy, short ragweed, and giant ragweed seemed most ideal. In addition, questionnaires were sent to relatives of the insane patients to determine the presence of allergy, how long it was noted, and what influence the mental imbalance produced, if any. Complete blood counts were also made on patients showing positive skin responses.

The patients who reacted positively to any of the pollens were then observed daily throughout the pollinating season of 1942 for symptoms of hay fever and asthma, and symptoms were checked by medical attendants between June 10 and September 10 on prepared charts. In all, there were 372 patients tested, representing thirteen different mental conditions, both organic and inorganic. Of these, fifteen or 4 per cent, reacted, from 3 plus to 4 plus, to scratch skin tests with the selected pollens.

TABLE I

SKIN TESTS OF 372 PSYCHOTIC PATIENTS

DIAGNOSIS	NUMBER TESTED	POSITIVE SKIN REACTION
Manic depressive	14	2
Dementia praecox	188	9
Involutional psychosis	10	
Mental deficiency	27	
Psychopathic personality	1	
Cerebral arteriosclerosis	49	3
Alcoholic deterioration	2	
Without psychosis	3	
Psychosis with syphilitic meningo-encephalitis	32	1
Senile psychosis with simple deterioration	16	
Epileptic deterioration	10	
Organic brain disease with Parkinson's syndromes	3	
Alcoholic psychosis	4	
Undiagnosed	13	
Total	372	15

One of the positive reactors had no clinical symptoms. Fourteen, or 3.7 per cent of the total tested, presented positive skin reactions, with hay fever observed objectively by us and by attendants. In some of these, the patients retained sufficient mentality to corroborate subjectively the clinical findings. There were three cases of asthma in the group, apparently due to pollen. One of these had been an inmate for ten years, and was hospitalized each September for the past eight years

because of asthma. With this exception, no other patient had ever complained to attendants or medical staff about hay fever or asthma.

There were 124 questionnaires returned by relatives of patients, or 33 per cent of those tested. Of these, four gave histories of hay fever, verified by us with skin tests and clinical observation. Three others gave a history of having had asthma before commitment, two of whom showed none when examined by us. The third patient had slight asthma accompanied by severe vasomotor rhinitis. He was a particularly deteriorated type on an arteriosclerotic basis, and had unusually severe nasal symptoms. The two most severe cases of hay fever occurred in patients with dementia praecox, one hebephrenic and the other catatonic, both greatly deteriorated. The catatonic patient presented constant drooling of the mouth during the hay fever season, clearing up when pollination ceased. Attendants stated that they had observed this occurrence for several years. A history of hives was given in three patients, one of whom presented hives at examination.

The amount of hay fever did not appear to have any relation to the degree of mental imbalance, nor to the presence or absence of organic disease. Severe and mild symptoms were present in both functional and organic groups, including cases of cerebral arteriosclerosis, dementia praecox of the various types, syphilitic meningo-encephalitis, and manic depressive insanity. During the middle of September, three of the hay fever patients developed typical asthmatic râles with cough and wheezing. These were found by routine examination of the positive skin reactors, not because of complaints of the patient. In all probability, routine examination of all patients including the skin-negative group would reveal other cases of asthma and vasomotor rhinitis. The patient with vasomotor rhinitis and asthma was discovered only because of information given in his questionnaire.

TABLE II

SUMMARY OF PATIENTS WITH POSITIVE SKIN TESTS TO POLLENS

PATIENT	CLINICAL DIAGNOSIS	DEGREE OF HAY FEVER	DEGREE OF ASTHMA	% EOSINOPHILES
1. M. B.	Manic depressive	++	1 attack before commitment	1
2. M. M.	Dementia praecox	++	0	4
3. S.	Manic depressive	++	0	10
4. E. B.	Syphilis meningo-encephalitis psychosis	++	0	1
5. H. B.	Dementia praecox	+++	++	Not done
6. I. C.	Dementia praecox	++	+	Not done
7. E. H.	Dementia praecox	++++	0	Not done
8. L. M.	Dementia praecox	++	0	3
9. I. L.	Dementia praecox	++	0	1
10. O. Z.	Dementia praecox	++	0	10
11. P. O.	Dementia praecox	++++	0	10
12. J. B.	Cerebral arteriosclerosis	++	0	1
13. J. L.	Cerebral arteriosclerosis	++	++	12
14. W. K.	Cerebral arteriosclerosis	+++	0	3
15. L. Z.	Dementia praecox	0	0	7

Differential blood counts were done on twelve of the fourteen patients having hay fever. Six of these revealed eosinophilia over 3 per cent, while one patient, with positive skin tests and no hay fever, had a 7 per cent eosinophilia. Nasal smears were not attempted.

Nine patients gave 1 to 2 plus skin reactions without evident hay fever. Of the 124 questionnaires returned, 36 indicated histories of headaches, ten of whom had, in addition, histories of hay fever or asthma in the immediate family. It would be difficult to establish an allergic etiology in this group of headaches, but the information is certainly suggestive in this direction in some of the cases. According to the questionnaires, two patients with hay fever and one with asthma were improved after commitment. On the other hand, two cases of asthma and one of hay fever were worse after commitment.

Since these findings compare about equally with the incidence of hay fever and asthma in the sane, they question the accuracy of commonly accepted statements as to the infrequency of hay fever and asthma in the insane. It would appear that a systematic allergic search will disclose as much allergy in the insane as in the sane. Furthermore, it is safe to say that, for the most part, the reason symptoms in the insane are not found is that the patient fails to complain; it is only the violently ill, such as the one case which was hospitalized yearly, who come to the attention of medical attendants. The impression that the psychotic loses his allergy because of environmental disinterest does not find substantiation in these studies.

SUMMARY

1. The incidence of hay fever and asthma in the insane, whether organic or inorganic, is the same as that in the sane.

2. The mental imbalance in the insane does not influence the degree of hay fever.

3. The low incidence of hay fever and asthma in the psychotic, quoted heretofore, is due probably to the failure of the insane to voice their complaints, and the lack of frequent, general, physical examination. Routine search for hay fever and asthma in the psychotic discloses as high an incidence as in the sane.

4. There is suggestive evidence that other forms of allergy besides hay fever and asthma are not uncommon in the psychotic.

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Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL FEINBERG, M.D., AND
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Letter to the Editor. Clearkin, P. A.: Lancet **1**: 509, 1943.

Clearkin, the government bacteriologist of British Guiana, writes that, contrary to the general opinion that hay fever is rare in the tropics, this ailment is found commonly in his territory and probably in other tropical localities. Bermuda grass is widely distributed in the coastal areas of British Guiana, and Barbados sour grass *(Andropogon panormitanus pertusis)* is second in importance. Rice and sugar cane pollen, although heavy, are also responsible for hay fever because of the strong trade winds. The cases are not seasonal, but diagnostic tests and treatment prove their specificity.

The Distribution and Pollination Times of the Important Hay Fever-Producing Plants in the United States. Gottlieb, P. M., and Urbach, E.: J. Lab. & Clin. Med. **28**: 1053, 1943.

The authors have gathered together the pollen surveys reported in various parts of the country. On the basis of these reports they have divided the United States into nine zones and have constructed pollinating calendars for each zone. Although this article is quite complete and extensive, it does not lend itself for abstract purposes, but those interested in hay fever conditions in any particular locality would gain materially by consulting this article.

Treatment of Asthma by Nicotinic Acid. Melton, G.: Brit. M. J. **1**: 600, 1943.

Of nineteen patients suffering from asthma, sixteen were relieved in some of their paroxysms by the intravenous use of from 50 to 100 mg. of nicotinic acid. The drug also appeared to be of some help if given orally three times daily in from 50 to 100 mg. doses over a protracted period. Of thirty patients treated orally, sixteen were benefited.

Blood Pressure Fluctuations in Bronchial Asthma. I. Clinical Observations. Osgood, H.: J. Lab. & Clin. Med. **28**: 927, 1943.

As in experimental bronchial obstruction, the author found in bronchial asthma wide fluctuations of the systolic blood pressure between expiration and inspiration. The high point of the pressure occurs during expiration, as it occurs in normal subjects, but the fluctuation between the two phases of respiration may be from 10 to 45 mm. Hg as compared with a normal 2 to 6 mm. Hg. It was found that the degree of fluctuation was roughly proportional to the severity of the asthma. Osgood concludes that this blood pressure fluctuation is a useful clinical guide to the degree of respiratory obstruction.

Use of New Ephedrine-Like Drug in Hay Fever and Asthma. Friedman, A. J., and Cohen, A. E.: Northwest Med. **43**: 138, 1943.

The ephedrine-like drug, nethamine hydrochloride (levo-1-phenyl-2-methylethylamine-1-propanol-hydrochloride) was given in twenty-three cases of asthma, with improvement in eleven. Of twenty-three patients suffering from hay fever, fourteen showed benefit. In a few patients in whom ephedrine failed to produce results, nethamine hydrochloride gave relief. The toxic effects were less with the new drug as compared to ephedrine. The ordinary therapeutic doses did not produce significant changes in blood pressure or pulse rate.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., AND MURRAY ALBERT, M.D., BROOKLYN

The Immunochemistry of Allergens. II. Antigenic Studies by the Dale Method of the Electrophoretic Fractionation Products of the Protein-Carbohydrate Fraction, CS-1A, From Cottonseed. Coulson, E. J., Spies, J. R., and Stevens, H.: J. Immunol. **46**: 347, 1943.

A protein-carbohydrate fraction (CS-1 or CS-1A) was previously isolated from cottonseed. This fraction possessed marked allergenic properties and could be further fractionated by chemical and electrophoretic methods into an active proteic component and active protein-carbohydrate complexes. The anaphylactogenic properties and the antigenic relationships of CS-1A and its electrophoretic fractionation products were studied by the Schultz-Dale technique. Four fractions were investigated in the present experiments. The first, an allergenic proteic fraction, CS-51R, was obtained by precipitation with picric acid from the cathode cell after electrophoresis of CS-1A. The second, CS-56R, an allergenic protein-carbohydrate fraction, was obtained by

precipitation with picric acid from the anode cell after electrophoresis of CS-1A. The third fraction, CS-56S, was obtained from the supernatant liquid after removal of the picrate derivative CS-56R. The fourth, CS-60C, was a carbohydrate-free protein obtained by electrophoretic refractionation of the cathode fractions of CS-1A. Virgin guinea pigs were sensitized by single subcutaneous injections of alum-precipitated solutions of unfractionated cottonseed and of its four fractions. The uteri of animals sensitized with unfractionated cottonseed extract reacted to CS-51R or CS-56R. Complete desensitization with these fractions did not completely desensitize to the whole extract, indicating the presence of more than one antigen in unfractionated cottonseed. When the uteri sensitized to the fractions CS-51R and CS-56R were desensitized with unfractionated cottonseed, subsequent tests with CS-51R or CS-56R failed to produce contractions. This indicates that these fractions are not derived proteoses, as they manifest no altered specificity in relation to unfractionated cottonseed. Fractions CS-51R and CS-56R appear to be performed native proteins. Fractions CS-51R and CS-56R are antigenically undistinguishable in crossed neutralization tests. Fraction CS-56S contained one antigen similar to CS-51R and another component unrelated to CS-51R and CS-56R. Fraction CS-60C, which was free of carbohydrate, manifested the same antigenic properties that CS-51R did. This indicated that the polysaccharides were not playing a part in determining the antigenic specificity of these fractions.

The Immunochemistry of Allergens. III. Anaphylactogenic Potency of the Electrophoretic Fractionation Products of CS-1A From Cottonseed. Coulson, E. J., and Spies, J. R.: J. Immunol. **46**: 367, 1943.

Since antigens differ in their sensitizing and shocking capacities, it was thought that the measurement of the anaphylactogenic capacities of the different fractions of cottonseed might serve as an aid in differentiating between antigenic activities which were not readily ascertainable by the Schultz-Dale technique. The anaphylactogenic potencies of the allergenic fractions CS-1A, CS-51R, CS-56, and CS-56R were studied. The LD 50 (median lethal dose) and SD 50 (median sensitizing dose) were calculated for each cottonseed allergenic fraction. The corresponding doses of crystalline ovalbumin were also determined for purposes of comparison. The LD 50 was that dosage of antigen which, when introduced by the intravenous route, would produce fatal anaphylactic shock in 50 per cent of previously sensitized animals. The SD 50 was the dosage of antigen which, when introduced by the intra-abdominal route, would sufficiently sensitize the animals so that a subsequent injection of a uniform, large dose of the antigen would induce fatal anaphylactic shock in 50 per cent of the animals.

Guinea pigs were sensitized by a single intra-abdominal injection of the test agent and tested intravenously after twenty-one days. A wide variation was found in the sensitizing capacities of the different cottonseed fractions and of ovalbumin. Fraction CS-56R, the high carbohydrate-containing fraction, had eight times the sensitizing capacity of CS-51R, the low carbohydrate-containing fraction. Since the antigenic specificity of these two fractions was the same, the greater sensitizing capacity of CS-56R was attributed to its large molecular structure because of its high carbohydrate content. Ovalbumin showed a sensitizing capacity ten times greater than CS-56R. The shocking capacities of the fractionation products of CS-1A and of ovalbumin were all of the same magnitudes when computed on the basis of their nitrogen content.

The Immunochemistry of Allergens. IV. Effect of Dilute Acid on Anaphylactogenic Activity, Specificity, and Reagin-Neutralization Capacity of Cottonseed Allergenic Fractions. Coulson, E. J., and Spies, J. R.: J. Immunol. **46**: 377, 1943.

The effect of dilute hydrochloric acid upon the anaphylactogenic activity, specificity, and reagin-neutralizing capacity of cottonseed allergenic fraction CS-1A was studied by means of the Schultz-Dale technique and by means of in vitro neutralization experiments. It had been previously shown that the allergenic activity of acid-treated fractions was unaltered when employed in testing cottonseed-sensitive patients. In cross neutralization experiments with the Dale technique, it was found that fraction CS-51R, when treated with acid, retained its antigenic specificity. However, acid-treated CS-51R did not have the same sensitizing or shocking capacity as the untreated CS-51 fraction. The shocking potency was diminished 54 per cent and the sensitizing capacity was diminished 78 per cent by acidification. Fraction CS-56, similarly, lost 66 per cent of shocking potency and 97 per cent of sensitizing capacity, when treated with dilute acid. However, fraction CS-56 suffered a slight alteration in specificity following acid treatment, although the original specificity still predominated. The in vitro reagin-neutralizing capacity of fraction CS-51R was markedly diminished (95 per cent) following acid treatment. It is concluded from these experiments that acid treatment alters the immunologic properties of the allergenic fractions of cottonseed by changing the structure of the molecule. The structural features of the molecule which determine its sensitizing capacity are different from those which determine its shocking capacity. The results also suggest that the structural features responsible for eliciting cutaneous reactions in cottonseed-sensitive individuals are not identical with those required for reagin neutralization.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Immunity to Tetanus Induced by a Third Dose of Toxoid Two Years After Basic Immunization: Based on a Study of Thirty-One Allergic Children. Peshkin, M. M.: Am. J. Dis. Child. **65**: 873, 1943.

The injection of a booster dose of alum tetanus toxoid two years after basic immunization was followed within one week by an adequate antitoxin response. This response was higher than that following basic immunization and lasted longer. It was also higher and more lasting than the response obtained in a group of children who received the booster dose only three to fifteen months after basic immunization instead of twenty-four months later.

Local reactions occurred in 50 per cent and febrile reactions in 22 per cent of the children in whom combined diphtheria tetanus alum toxoid was given as the booster dose. Local reactions occurred in 25 per cent of the children in whom only tetanus alum toxoid was given, and there were no febrile reactions. In all instances, scratch tests with the combined toxoid were negative. One child showed a general allergic reaction after the combined toxoids. It consisted of fever, urticaria, malaise, and vomiting. It was the only general reaction encountered in 186 allergic children who had had from two to five doses of combined toxoid.

In view of these data, tetanus toxoid alone rather than combined toxoid is advised for the late recall dose.

Statistical Investigation of Bronchial Asthma in Children. Brock, J.: Deutsche med. Wchnschr. **46**: 1120, 1942.

The following conclusions were reached in investigating 351 children, 2 to 15 years of age, who had been to Bad Dürkheim in the Black Forest because of asthma: (1) In the great majority, the asthma began in the first six years of life—predominantly from 2 to 4 years of age; (2) one-half of the children had an early history of eczema or milk crust. These patients tended to an earlier onset, but not to a more severe type, of asthma; (3) after the age of 10 years is reached, there is a tendency to improve, especially noticeable at puberty, at which time a third of the children made a spontaneous recovery. Most of the remainder improved at this time so that only 20 per cent entered adulthood uninfluenced by increasing age; (4) in the climate of Bad Dürkheim, with its elevation of 2,400 feet, 94 per cent of the asthmatic children are entirely free of asthma; (5) a beneficial aftereffect of a stay at Bad Dürkheim (usually 6 weeks in duration) was evident in 3 out of 4 children. The duration of the benefit was 1½ years or more in one-half these children. In 14 per cent it amounted to a cure in that no further signs of asthma appeared.

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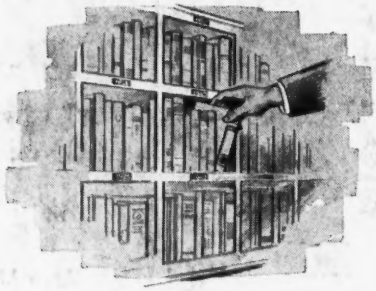

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